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OSTEOPOROSIS ASSOCIATED WITH LOW SERUM PHOSPHORUS AND RENAL GLYCOSURIA

W. T. COOKE, M.D., F.R.C.P. (Lond.)

J. A. BARCLAY, M.B.

A. D. T. GOVAN, M.B., Ph.D.
AND
L. NAGLEY, M.D., M.R.C.P. (Lond.)
BIRMINGHAM, ENGLAND

WE ARE presenting the history and investigations concerning a patient with progressive decalcification, a low serum phosphorus content and renal glycosuria. The findings suggest that a physiologic defect of the renal tubules is the primary cause for certain osteoporotic conditions of obscure origin.

REPORT OF A CASE

D. L., a man aged 39 years at death, was born at St. Davids, Pembrokeshire, in 1906, the seventh child of a family of nine, the other members being four brothers and four sisters.

As a child he was considered to be healthy and strong. His father died in 1914 of a gastric ulcer, and his mother died (after World War I) of meningitis. Seven of the family are dead, six of tuberculosis and the seventh from an accident. The youngest brother is well.

When aged 22, after a severe infection of the throat stiffness developed in his back and muscles, which passed off in one month. From that time on he was in and out of employment, living on an inadequate diet and going without food on many days. In 1932 he noticed that he had difficulty in straightening himself and was having much generalized pain. He also complained of weakness of his legs, so that he occasionally stumbled and fell if he caught his foot on the ground. About this time he moved to Birmingham, and since his health had not improved he was admitted to a hospital and treated for rheumatism. Following his discharge from the hospital, he found himself no better, and after further falls he was admitted to the Birmingham Infirmary, where he was treated with sodium gold thiomalate ("myocrysin") but was unable to finish the course because of a severe cutaneous reaction. At this period (1933) he was only able to walk with the aid of two sticks. His back was painful, and during the next few years his condition gradually got worse. However, roentgenograms of the skeleton taken in 1934 revealed no abnormality of the bones, and a note in 1936 stated that no deformity of the bones was seen. In 1938, during a mild infection of the upper

From the Departments of Medicine, Physiology and Pathology, Birmingham University and the Birmingham Infirmary.

respiratory tract, with pyrexia and cough, a deformity of the sternum developed overnight. His legs became weaker, so that he was semibedridden. He was unable to raise his arms above his shoulder, and in 1939 tremor of the legs appeared. He had numerous postural aches and pains, was tender to touch and had much discomfort following muscular contractions. He had always drunk much tea, and this habit was more marked in recent years, but he did not often need a drink during the night. He micturated at 8 p. m. on retiring, again before midnight, but not again until morning. He had occasional mild cramps, with some numbness and tingling of his hands, and also periods of mental depression. He had no soreness of the tongue or mouth. His bowel habits were regular, and the stools were well formed and colored.

He had never had a large appetite and usually neglected breakfast. While out of work, though food was scarce, he had always tried to get one meal during the day; nevertheless, even when in work, he frequently missed his meals. He had never liked milk. Since the beginning of the war he had had no extra milk, and although the diet in the infirmary provided 27 ounces (755 cc.) per day, he

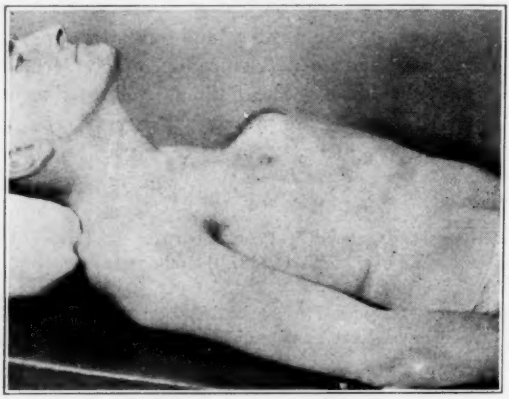

Fig. 1.—Photograph showing the deformity of the sternum.

frequently did not drink this quantity. He was 70 inches (178 cm.) tall and weighed 146 pounds (66 Kg.).

In March 1942 he was admitted to the Queen Elizabeth Hospital for further investigation, complaining of general weakness, pain in his muscles on exertion and pain in the back. Examination at the time showed an intelligent and well spoken man, cooperative, weighing 103 pounds (46.5 Kg.). The mouth was healthy; several teeth had been extracted. The spine was twisted, and movement appeared to be restricted in all directions, but examination was difficult. There was a deformity of the sternum, the manubrium sterni appearing to be in the normal position while the sternum itself was bent forward to give the appearance of an actual tumor (fig. 1). Impingement of the lower ribs on the iliac crests demonstrated the shortening of the spine. The remainder of the bony skeleton appeared to be of normal shape and to have no abnormal tumors. It was not tender to percussion in any area.

The skin was dry and scaly, and there were numerous erythematous areas, especially on the chest. The power in all groups of muscles was much greater

than might have been expected, but the patient was prevented from exerting his maximum strength by the pain that contraction caused. The greatest amount of pain seemed to arise during the phase of relaxation.

No clinical abnormality could be detected in the lungs, and it was impossible to make out the size of the heart owing to the gross deformities that were present. There was a harsh systolic murmur over the pulmonary area. The blood pressure was 115 systolic and 80 diastolic. The liver was not palpable. There was a semisolid rounded lump the size of an orange between the left costal

Fig. 2.—Thoracic and lumbar regions of the spine, showing osteoporosis and varying degrees of collapse.

margin and the iliac crest, which was tender on palpation. There was no alteration in reflexes, and no abnormality in sensation could be detected. The sphincters were normal.

The red blood cell count was 4,720,000 and the hemoglobin content 98 per cent. The white blood cells numbered 5,050 with 61.3 per cent polymorphonuclear cells, 1.0 per cent eosinophils, 26.7 per cent lymphocytes and 11.0 per cent monocytes. The urine contained no albumin, but there was inconstant glycosuria, while a urea clearance test showed a standard clearance of 54 cc. per minute, i. e., 96 per

cent of normal, in the first hour and 75 cc. per minute, i. e., 138 per cent of normal, in the second hour, with a blood urea content of 35 mg. per hundred cubic centimeters. A fractional test meal showed hyperacidity.

Initial analyses of the blood showed a plasma carbon dioxide-combining power of 55 volumes per cent, a plasma p_H of 7.32, a serum sodium chloride content of 600 mg., a calcium content of 10.3 mg. and a phosphorus content of 2.2 mg. per hundred cubic centimeters. The serum phosphatase level was 16.6 units (Jenner and Kay). The percentage of fat in dried feces was 19.8.

Fig. 3.—Right femur, showing osteoporosis, thinning of the cortex and preservation of normal striations of the bone.

Roentgenograms of the skull, humerus, spine, femurs and hands showed extensive osteoporosis; fractures of the ninth and tenth ribs were shown. There was no evidence of formation of cysts. The roentgenologic study was repeated after the patient had been two months on a diet containing 4 Gm. of calcium and 32,000 to 200,000 units of vitamin D daily. No change could be detected (figs. 2 and 4).

The details of investigations on calcium and phosphorus metabolism are given in table 1 and figure 5.

At the end of this period of observation, certain points were noted. With varying intake of calcium and large doses of vitamin D, the urinary excretion of calcium remained relatively low. The serum phosphorus content, contrary to the usual occurrence with vitamin D therapy, was depressed, while the urinary excretion of phosphorus was increased. Because of these findings, hyperparathyroidism appeared unlikely, and the absence of symptomatic improvement with vitamin D therapy and adequate diet was against a diagnosis of osteomalacia. A possibility remained that the patient's kidney was unable to reabsorb phosphate to allow of adequate levels of serum phosphorus. He was, therefore, discharged to await the development of suitable methods of investigation of this problem.

He was again admitted to the Queen Elizabeth Hospital on Aug. 20, 1943. His general condition was essentially unchanged, though roentgenograms sug-

Fig. 4.—Pelvis, showing osteoporosis, deformity of the pelvic brim and bilateral coxa valga.

gested that further decalcification had taken place. During the whole time he was in the hospital, glycosuria was present. A glucose tolerance test showed a fasting blood sugar content of 85 mg. and then 145, 140, 115 and 75 mg. per hundred cubic centimeters at subsequent half-hour intervals. Sugar was present in large amounts in the specimens taken after one and two hours. Examination of the urine showed no other abnormality and no cystine crystals. The initial examination of the blood showed a plasma carbon dioxide-combining power of 52.5 volumes per cent, a plasma p_H of 7.20 and a plasma sodium chloride level of 573 mg. per hundred cubic centimeters. The serum albumin content was 5.0 Gm., the globulin content 2.9 Gm. and the serum calcium and phosphorus levels

9.5 and 0.8 mg. per hundred cubic centimeters; the serum phosphatase level was 20.9 units. A blood count showed 4,560,000 red blood cells, with a hemoglobin content of 90 per cent, and 7,300 white blood cells.

Further studies on excretion of calcium and phosphorus (tables 1 and 2) showed no essential changes from those carried out during the patient's first stay in the hospital.

Clearances of inulin and Diodone (the diethanolamine salt of 3,5-diiodo-4-pyridone-N-acetic acid) were studied on two occasions during the intravenous administration of inulin and Diodone [1] and on the third occasion after the serum level of phosphorus had been raised by infusion of 400 cc. of isotonic solution of phosphate.

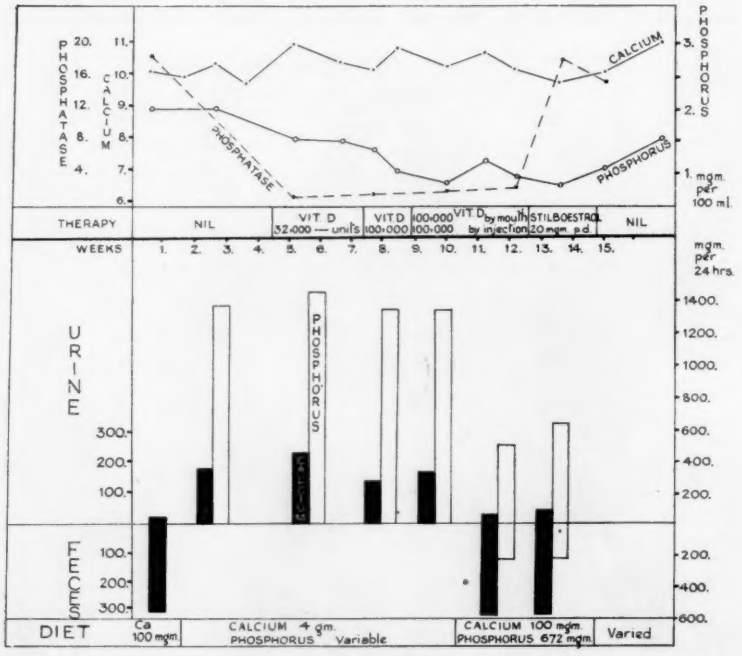

Fig. 5.—Chart showing the effects of diet and therapy on the calcium and phosphorus levels in the blood, urine and feces.

Clearance of inulin (eleven observations) averaged 93 cc. per minute (normal clearance, 90 to 120 cc.). The plasma clearance (ten observations, three experiments) averaged 522 cc. per minute and that in the blood flow 822 cc. per minute (normal for plasma but low for the blood flow, possibly due to overhydration causing a low hematocrit value).

The maximal rate of tubular excretion of Diodone was determined on one occasion, being 34 mg. per minute—a low normal value. Clearances of glucose

1. Smith, H. W.; Goldring, W., and Chasis, H.: Measurement of Tubular Excretory Mass, Effective Blood Flow and Filtration Rate in Normal Human Kidney, J. Clin. Investigation **17**:263, 1938.

were determined in two experiments, from which the tubular excretion of glucose was calculated to be 112 mg. per minute (normal clearance, 200 to 300 mg. per minute). Clearance of phosphate was determined over seven periods, averaging 42 cc. per minute at a plasma level of 1.2 mg. of phosphorus (clearance of phosphate at normal plasma levels is 4 to 6 cc. per minute). In two periods, with the plasma level between 1.2 and 13 mg. of phosphorus, the clearance of phosphate exceeded that of inulin, viz., phosphate, 100 cc. per minute and inulin, 76 cc. per minute.

The interrelation between glucose and phosphorus levels in the blood was also followed.

Finally, the possibility that an acid urine might play some part in the poor absorption of phosphate was studied, and urine was collected under paraffin over twenty-four hours.

Random sampling on five separate days showed a varying p_H of 6.2, 5.8, 6.0, 5.2 and 5.6, the daily intake of fluid during the period of three weeks averaging 1,700 cc.

TABLE 1.—*Glucose and Phosphorus Levels in the Patient's Blood*

	Fasting	½ Hr.	1 Hr.	1½ Hr.	2 Hr.	2½ Hr.
Glucose.....	70	150	125	100	65	55 mg. per 100 cc.
Phosphorus.....	0.7	0.7	0.8	0.6	0.8	1 mg. per 100 cc.

TABLE 2.—*Results of Examination of Urine*

Specimen	Volume, Cc.	Hydrogen Ion Concentration	Ammonia, Total N/10 Acid
1.....	405	4.97	120
2.....	440	5.48	61
3.....	130	5.13	36.6
4.....	335	5.32	148
Total.....	1,310		365.6

Owing to the lack of beds at this point, it became necessary to transfer the patient back to the infirmary (Oct. 30, 1943). His condition remained stationary until June 1945, when symptoms of a peptic ulcer developed. On July 9, 1945 he had hematemesis. In spite of strict treatment for ulcer, his condition did not improve, and on August 28 he had further melena and showed signs of continued bleeding. Following transfusion, he improved slowly until October 7, when a further hematemesis proved fatal.

Gross Observations at Autopsy.—Owing to legal formalities, postmortem examination could not be carried out until four days after death, the body being kept in the refrigerator in the mortuary. The body was that of a pale man with deformity of both legs, kyphosis, scoliosis and lordosis of the spine, particularly in the thoracic region, and a definite bulging of the central portion of the center of the sternum.

The head appeared to be slightly increased in size. All bones were soft. The ribs showed reduction in the compact bone and could be distorted easily, the bone being extremely soft. The bodies of the vertebrae were similarly affected. A knife could be easily inserted into the substance of the bone.

There was a cystic swelling present in the left side of the loin.

Thorax.—The trachea and bronchi were normal. There were some adhesions between the right apex and the wall of the chest. This small area appeared to be a healed focus of tubercle. The lungs (weight, 1,008 mg.) were extremely edematous but were otherwise normal. The thyroid gland was normal in size. The parathyroid glands were normal (5 by 2 by 3 mm.), and the approximate total weight of four glands was 175 mg. The heart (weight, 448 Gm.) was enlarged, with hypertrophy of the right ventricle. The muscle was extremely pale, with thrush-breast mottling.

Abdomen.—The liver (weight, 1,288 Gm.) was pale. The spleen (weight, 72 Gm.) was normal in size and rather firm. The adrenal glands showed slight opacity in the medulla. Both kidneys (weight, 168 Gm. each) were extremely pale. The testes were small but were otherwise normal. The stomach was

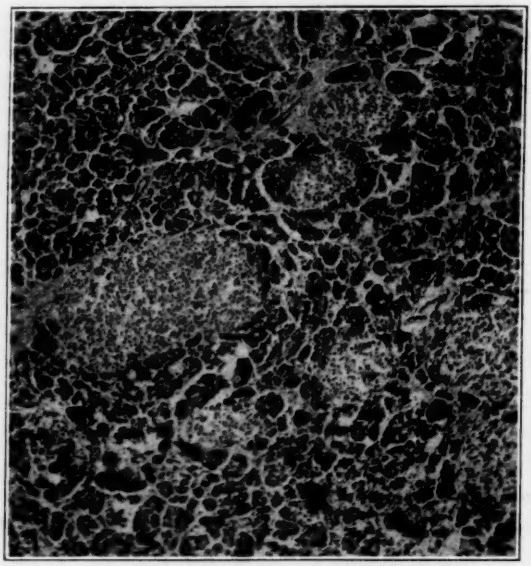

Fig. 6.—Representative section of the pancreas. Note the large amount of islet tissue. Stain, hematoxylin and eosin; × 60.

slightly distended with altered blood. In the first part of the duodenum there was a large chronic ulcer eroding into the head of the pancreas. The pancreas appeared normal.

Head.—The brain (weight, 1,456 Gm.) showed slight edema. The vessels were healthy. The pituitary gland appeared to be normal. The bones of the skull were soft, but without undue thickening.

The swelling in the left side of the loin was between the internal oblique and transversalis muscles, and when incised it was cystic, with irregular walls, and appeared to be an old hematoma.

Histologic Examination.—Parathyroid Glands: The microscopic appearances of the parathyroids showed no evidence of hyperplasia (fig. 7).

Pancreas: The glandular portion of the pancreas appeared normal. The islets, however, were increased in number and size, comprising about one tenth of the field in sections taken from various parts of the organ and, in a few instances, as much as one third (fig. 6).

Adrenals, Pituitary, Testes, Thyroid Gland and Spleen: These showed no evident microscopic abnormality.

Liver: The lobules of the liver showed a coagulative necrosis of the central zone, and there was a slight polymorphonuclear reaction in the associated vessels. Widespread fatty change was present both in the central necrotic zones and in the outer zones. No trace of glycogen could be found in any part. A normal positive phosphatase reaction was given by the bile capillaries of the outer zones when tested by Gomori's method.

Kidneys: A generalized change was obvious in the epithelium of the first convoluted renal tubules. The lumens were full of granular debris. The cells showed pronounced vacuolation; in some the vacuoles were small, giving a

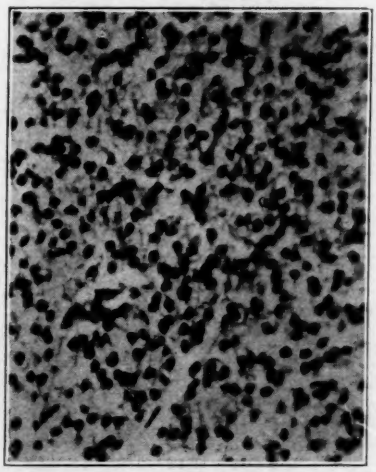

Fig. 7.—Section of the parathyroid gland. There is no sign of hyperplasia and none of the acinar formation or colloid secretion usually associated with hyperactivity. Stain, hematoxylin and eosin; × 320.

foamy appearance to the cytoplasm, while in others the cytoplasm was reduced to a film covering a single large vacuole (fig. 8). In every tubule occasional necrotic cells could be found; in a few the whole epithelial lining appeared to have undergone necrosis, with pyknosis of nuclei. These changes were confined to the first convoluted tubules and were not generalized, as one might reasonably expect them to be if they had been due to postmortem change. Regeneration had occurred in parts, the epithelium being either in the form of basophilic cells with hyperchromatic nuclei or larger and frequently multinuclear basophilic masses with similar hyperchromatic nuclei. There was a general increase of connective tissue in the kidney, with thickening of basement membranes of both tubules and glomeruli, but foci of more decided fibrosis could be seen near glomeruli in relation to the second convoluted tubules (fig. 9) and at the junction of the cortex and medulla. Where fibrosis was present in the latter situation, the tubules had

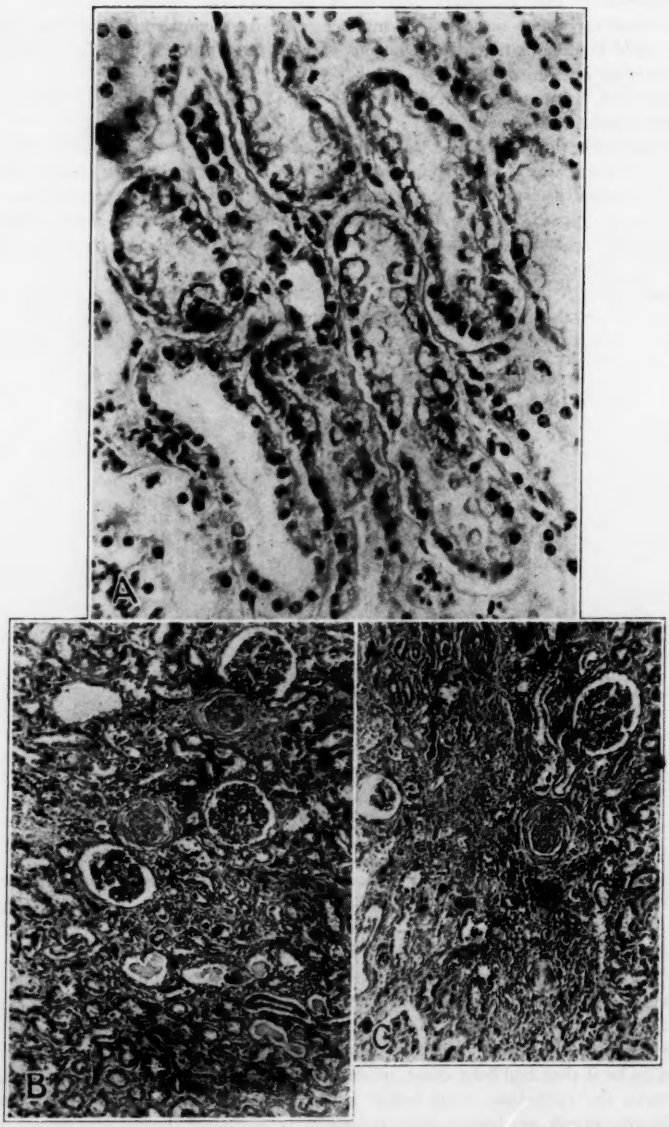

Fig. 8.—Photomicrographs of the kidney. Stain, hematoxylin and eosin. *A*, extreme vacuolation and degenerative changes in first convoluted tubules (× 320). *B*, low power view of kidney showing focal fibrosis around second convoluted tubules (× 60). *C*, section of kidney showing fibrous obliteration of ascending limbs of Henle (× 60).

almost completely disappeared. In some cases the relative glomerulus had become hyalinized and the first convoluted tubule had undergone replacement fibrosis. A few colloidal casts were present in the ascending limbs of Henle. Staining with sudan dyes revealed a mild degree of fatty degeneration of the broad ascending limbs of Henle. The arteries showed some fibrosis of the media, but there was none of the arteriolar endarteritis usually associated with primary arteriosclerosis. Apart from the hyalinized glomeruli, the glomerular capillaries were normal.

Tests for sites of phosphatase activity revealed that this was practically absent. Only an occasional first convoluted tubule gave a faintly positive reaction.

Bone: Sections of bone from the femur showed a definite reduction in the thickness of the cortex; the subperiosteal layer was broken up into interlacing trabeculae resembling cancellous bone. At many points there were surface depressions containing dilated vessels, and the bone itself appeared to have lost a considerable amount of calcium. In a few places there were small masses of osteoid tissue

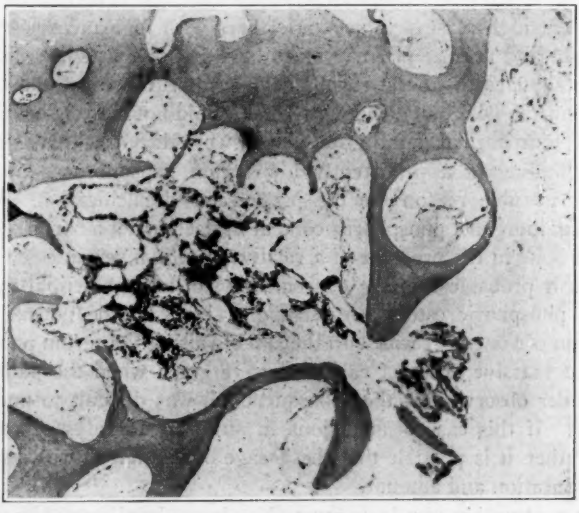

Fig. 9.—Section of bone showing thinning of trabeculae and increase in diameter of canals. Some loss of staining power at the edge of the bony trabeculae is just discernible. Stain, hematoxylin and eosin; × 60.

and occasional osteoclasts, but the major change appeared to be a gradual atrophy. In the interior of the bone the trabeculae were much thinner than normal, staining bright pink instead of the normal basophilic color. This change was most noticeable at the edges of the trabeculae next to dilated vessels. No sign of activity of osteoclasts or of osteitis fibrosa could be seen in this part.

COMMENT

The presenting feature in this case was a slowly progressive osteoporosis. At first sight, the most logical explanation for this was the long and continued dietary deficiency in the years prior to the onset of the patient's symptoms, but the subsequent failure to respond to an

adequate diet and vitamin D rendered such a cause unlikely. Moreover, roentgenologically the bones had preserved their cancellous structure, a feature not usually noted in osteomalacia. Similarly, histologic examination of the various bones suggested only an extensive decalcification and not the excessive osteoid tissue of osteomalacia. Such a degree of osteoporosis may be seen in well defined conditions such as hyperparathyroidism, hyperthyroidism and chronic renal disease and in the persistent acidosis of certain cases of nephrocalcinosis,[2] in Fanconi's syndrome,[3] and in steatorrhea. All of these, however, with the possible exception of hyperparathyroidism, were ruled out by the laboratory investigations. The persistently low urinary excretion of calcium in the presence of a normal plasma level made the diagnosis of hyperparathyroidism unlikely. Nevertheless, cases with low urinary excretion of calcium but high plasma values and others with high urinary excretion of calcium and normal plasma values have been reported,[4] and in view of some similarities in the roentgenologic appearances of the bones of our patient the possibility, though remote, could not entirely be dismissed until the four normal parathyroid glands were demonstrated at autopsy.

The finding of a persistently low serum phosphorus content suggested a possible reason for the progressive decalcification. While a low serum inorganic phosphorus content in itself is not a bar to the laying down of bone in the presence of a relatively normal serum calcium level, it makes it probable that the concentration of more essential materials, such as phosphoric esters, are lacking to keep up the normal rate of deposition of bone.[5] It was with the aim of raising the serum phosphorus level that massive doses of calciferol were given when the patient first came under observation; the subsequent fall was difficult to understand (fig. 5). If this case is analogous in any way to cases of refractory rickets,[6] then it is possible that the dosage of vitamin D was insufficient both in duration and amount.

Any explanation of a low serum phosphorus level cannot be complete unless the role played by the kidney is considered. In our patient there was no disturbance of renal function as judged by standard tests, but

2. Albright, F.; Consolazio, W. V.; Coombs, F. S.; Sulkowitch, H. W., and Talbott, J. H.: Metabolic Studies and Therapy in Case of Nephrocalcinosis with Rickets and Dwarfism, Bull. Johns Hopkins Hosp. **66**:7, 1940.

3. Fanconi, G.: Nondiabetic Glycosuria and Hyperglycemia in Older Children, Jahrb. f. Kinderh. **133**:257, 1931.

4. Snapper, I.: Medical Clinics on Bone Diseases: Text and Atlas, New York, Interscience Publishers, Inc., 1943.

5. Robison, R.: The Significance of Phosphoric Esters in Metabolism, New York, New York University Press, 1932. Kay, H. D.: Phosphatase in Growth and Disease of Bone, Physiol. Rev. **12**:384, 1932.

6. Albright, F.; Butler, A. M., and Bloomberg, E.: Rickets Resistant to Vitamin D Therapy, Am. J. Dis. Child. **54**:529 (Sept.) 1937. Bakwin, H.; Bodansky, O., and Schorr, R.: Refractory Rickets, ibid. **59**:560 (March) 1940.

when the excretion of glucose and phosphorus were specifically considered it was clear that these functions of the kidney were abnormal.

With normal clearance of inulin and with a maximal tubular excretion of glucose of only 112 mg. per minute, glycosuria must exist at all normal levels of blood sugar. In our patient we were not able to determine whether the absence of sugar in the urine at certain periods was due to a phase of decreased rate of glomerular filtration or to a rise of the maximal tubular absorption of glucose since sugar was always present in the urine during the times we were carrying out our tests.

The daily excretion of phosphate and the studies of phosphate clearance suggested that the kidney was unable to handle phosphate normally. The defect might well be considered as poor reabsorption of phosphate alone, but the findings during the periods of raised serum phosphate content ruled out such a simple explanation. In this experiment, clearance of phosphate at raised plasma levels exceeded that of inulin, so that phosphate must therefore be secreted. In dogs, phosphate is secreted from plasma levels of about 6 mg. per hundred cubic centimeters, and there is inferential evidence that the same phenomenon occurs in human beings.[7] Even so, the data in our case are insufficient to decide which factor is the more important, defective absorption or abnormal secretion.

The fact that autopsy could not be carried out until four days after death detracts from the value of the postmortem observations. Nevertheless, it was possible to demonstrate without normal parathyroid glands, some hypertrophy of the islets of Langerhans, abnormal thinning of the bony cortex and a large chronic duodenal ulcer. Some of the general changes in the liver and kidney were no doubt due to postmortem autolysis, but this would not account for many of the focal changes in these organs, such as the central necrosis of the liver. Similarly, in the kidney, changes were confined almost entirely to the first and second convoluted tubules, and the fibrosis present was evidence of a long-standing condition. If such changes are accepted as having existed prior to death, then some pathologic evidence is offered in support of our hypothesis. It may be significant that the part of the nephron which showed extensive vacuolation and almost complete absence of phosphatase has been associated with reabsorption of phosphate.[8] The distal nephron has been related to the reabsorption of sodium and acidification of the urine,[9] and McFarlane [10] has shown that

7. Barclay, J. A.; Cooke, W. T.; Kenney, R. A., and Nutt, M. E.: Phosphate Excretion in Man and Dog, read before the Physiological Society, 1946.

8. Smith, H.: Physiology of Kidneys, ed. 2, New York, Oxford University Press, 1943.

9. Pitts, R. F., and Alexander, R.: Renal Reabsorptive Mechanism for Inorganic Phospate in Normal and Acidotic Dogs, Am. J. Physiol. **142**:648, 1944. Footnote 8.

10. McFarlane, D.: Experimental Phosphate Nephritis in Rat, J. Path. & Bact. **52**:17, 1941.

the excretion of excess acid phosphate will cause necrosis and resulting fibrosis in this area. Since large quantities of phosphate were being excreted in an acid urine, the epithelial degeneration and associated fibrosis in the distal tubules in our case may well be due to a similar mechanism.

There are insufficient data to do more than draw attention to the relationship between phosphate and glucose levels in the blood [11] and to suggest that the hypertrophy of the islets of Langerhans may have been a compensatory phenomenon.

SIMILAR CASES IN THE LITERATURE

Milkman [12] reported a case of a 40 year old woman whose condition he considered to represent a distinct clinical syndrome. She had suffered with progressive disorders of the bones over a period of eight years, the prominent features being lumbosacral pain, general weakness, difficulty in raising the legs to climb stairs, tenderness over the bones, especially those of the chest and pelvis, increased patellar reflexes and sclerotic changes in the bones resembling osteomalacia or late rickets. Roentgenograms revealed the presence of many transverse breaks or pseudofractures. The serum calcium varied between 15 and 10 mg. (more usually around 10 mg.) and the serum phosphorus between 2 and 6 or 8 mg. per hundred cubic centimeters (more usually around 2). There was also inconstant glycosuria, but no albuminuria. At autopsy "diffuse nephritis with arteriosclerotic changes" was noted. Sections from the left femur "did not resemble osteomalacia." All the involved osseous tissue showed strikingly increased vascularity; sections had to be cut with a saw except at the affected parts. The parathyroid glands were normal.

Michaëlis [13] reported the case of an 18 year old youth with progressive softening of the bones. The serum calcium was within normal limits, but the serum phosphorus was low—1.8 to 2.0. A number of biopsies were made to exclude the possibility of the presence of myeloma, but the exact architecture of the bone was not studied in detail. Exploration revealed normal parathyroid glands. Vitamin D and a high calcium diet were totally ineffective.

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11. McLeod, J. J. R.: Carbohydrate Metabolism and Insulin, London, Longmans, Green & Company, Ltd., 1926. Reiser, R.: Phosphorus Changes During Absorption of Oil and Glucose, J. Biol. Chem. **135**:303, 1940. Hanes, F. M., and Reiser, R.: Relation of Phosphorus to Fat and Glucose Metabolism in Sprue, Am. J. M. Sc. **200**:661, 1940. Kaplan, N. O., and Greenberg, D. M.: Action of Insulin on Phosphate Cycle, J. Biol. Chem. **156**:553, 1944.

12. Milkman, L. A.: Pseudofractures (Hunger Osteopathy, Late Rickets, Osteomalacia): Report of Case, Am. J. Roentgenol. **24**:29, 1930; Multiple Spontaneous Idiopathic Symmetrical Fractures. ibid. **32**:622, 1934.

13. Michaëlis, L.: Systemic Disease: Case, Fortschr. a. d. Geb. d. Röntgenstrahlen **45**:187, 1932.

Leedham-Green and Golding [14] reported the case of a 34 year old woman with progressive deformity of the bones, multiple symmetric pseudofractures and diffuse osteoporosis. The serum calcium was 9.6 mg. and the serum phosphorus 2.2 to 2.8 mg. per hundred cubic centimeters, with a blood phosphatase value of 30 units. The authors discussed the question of terminology and proposed the use of the term osteoporosis melolytica or osteoporosis meloclastica.

Edeiken and Schneeberg [15] made extensive observations on a 34 year old woman with numerous fractures. The disorder had arisen in childhood, and when first seen she was complaining of cramplike pains in the left thigh and of painful waddling gait. Roentgenographic examination showed fractures of both clavicles, the axillary border of the scapulas, the right radius and ulna, the left ulna, numerous ribs, both femurs, the right tibia and the left fifth and right third metatarsal bones. The serum calcium varied between 11.0 and 9.3 mg. and the phosphorus between 2 and 2.6 mg. per hundred cubic centimeters, and the phosphatase was slightly elevated. The urea clearance test showed a clearance of 73 per cent, with a blood urea content of 17 mg. per hundred cubic centimeters. Fishberg's concentration test showed specific gravities of 1,012, 1,011 and 1,012. The plasma carbon dioxide-combining power was 47 per cent and the serum chloride content 610 mg. per hundred cubic centimeters. The urine contained no albumin but showed intermittent glycosuria, without abnormal levels of sugar in the blood. The calcium balance test, with the patient on a 500 mg. intake of calcium, showed a slight negative balance and a low output of calcium in the urine.

The authors reviewed 19 other cases which they considered to be similar to their case. In all, the characteristic features were pain, disturbance of gait and the roentgenologic appearances of multiple transparent bands or pseudofractures, symmetrically located in various portions of the skeleton and usually interpreted as fractures. To cover this group of symptoms, they considered that the term "milkman's syndrome" should be retained until a definite etiologic agent was determined.

In all these cases the crucial point in the diagnosis has been the roentgenologic findings, in particular the presence of pseudofractures, and little attention has been paid to the biochemical features and the possible etiologic role of the kidneys. Camp and McCullough [16] pointed

14. Leedham-Green, J. C., and Golding, F. C.: Osteoporosis Melolytica ("Multiple Spontaneous Idiopathic Symmetrical Fractures"), Brit. J. Surg. **25**: 77, 1937.

15. Edeiken, L., and Schneeberg, N. G.: Multiple Spontaneous Idiopathic Symmetrical Fractures: Milkman's Syndrome, J. A. M. A. **122**:865 (July 24) 1943.

16. Camp, J. D., and McCullough, J. A. I.: Pseudofractures in Diseases Affecting the Skeletal System, Radiology **36**:651, 1941.

out that pseudofractures are found in many diseases of the bones, and they listed more than fourteen conditions in which pseudofractures may occur; hence the mere presence of pseudofractures may be ruled out of discussion. In the cases reported by Garcin, Legrand and Bernard [17] and Leriche and Jung,[18] evidence is insufficient to establish their relationship to the case we are reporting. In others, the findings suggest other possible etiologic factors, such as hyperthyroidism,[19] chronic renal disease [20] and osteomalacia.[21] Lombard and Tillier [22] reported the case of a 32 year old man, first seen by them at the age of 15. He was the fourth and only surviving son of a deformed mother. Osteotomies were performed at that time, when it was noted that the bones were excessively soft. The patient remained well and able to work and earn his living until the age of 32. At that time roentgenograms revealed the presence of forty-three pseudofractures. Chemical examination of the blood revealed a blood urea content of 53 mg., a cholesterol content of 278 mg., a calcium level of 9.6 mg. and a phosphorus level of 4.2 mg. per hundred cubic centimeters. This case had some features similar to those of our case, but the findings just prior to death suggested definite renal impairment similar to that in cases reported by Snapper.[4]

Fanconi,[23] in investigating a number of obscure metabolic upsets associated with resistant rickets in childhood, suggested that some might be associated with a functional defect of the renal tubules. He has reported a number of such cases associated with retention of chlorides and low phosphate content. McCune, Mason and Clarke [24] have reviewed these conditions, especially in respect to their occurrence in childhood.

17. Garcin, R.; Legrand, G., and Bernard, P.: Milkman Syndrome of Unknown Etiology: Clinical Cure and Roentgen Improvement Under Influence of Vitamin and Calcium Therapy, Bull. et mém. Soc. méd. d. hôp. de Paris **53**:1166, 1937.

18. Leriche, R., and Jung, A.: Spontaneous Nontraumatic Osseous Fissures of Undetermined Origin: Case, Lyon chir. **35**:47, 1938.

19. Guillain, G.; Lereboullet, J., and Auzépy, P.: Milkman Syndrome (Multiple Symmetrical Striae of Resorption): Nosographic Considerations; Case, Bull. et mém. Soc. méd. d. hôp. de Paris **53**:879, 1937.

20. Ravault, P. P.; Girard, M., and Didierlaurent: Symmetrical Spontaneous Fissuration (Milkman Syndrome), Lyon méd. **162**:189 and 217, 1938.

21. Debray, M.; Andre, T., and Gireaux: A Case of Multiple Spontaneous Fractures Difficult to Classify: Nosologic Discussion, Bull. et mém. Soc. méd. d. hôp. de Paris **49**:1038, 1933. Debray, M.: Chronic Painful Osteopathy with Multiple Symmetrical Pseudofractures: Case, ibid. **56**:573, 1940.

22. Lombard, P., and Tiller, H.: Spontaneous Fissuration of the Skeleton, Mém. Acad. de chir. **64**:336, 1938.

23. Fanconi, G.: Nephrotic-Glycosuric Dwarfism with Hypo-nephrotisch-glykosurische Zwergwuchs mit hypophospha-phasphatemic Rickets, Jahrb. f. Kinderh. **147**:299, 1936; footnote 3.

24. McCune, D. J.; Mason, H. H., and Clarke, H. T.: Intractable Hypophosphatemic Rickets with Renal Glycosuria and Acidosis (Fanconi Syndrome): Report of Case in Which Increased Urinary Organic Acids Were Detected and Identified with Review of Literature, Am. J. Dis. Child. **65**:81 (Jan.) 1943.

In 1935 Hunter [25] reported two cases essentially similar in detail to our case. The first was that of a 29 year old man who had suffered with repeated fractures of the superior ramus of the ischiatic bone, the left femur, the right ulna and the right tibia and right fibula, all being affected at various times. The serum calcium varied between 10.0 and 8.9 mg. and the serum phosphorus between 1.1 and 1.6 mg. per hundred cubic centimeters. The roentgenograms showed excessive decalcification of the bones. Renal glycosuria was constant.

The second case was that of a 35 year old man who presented severe and disabling pains in the bones, which had come on over a period of six months. The roentgenograms were similar to those in the first case. Renal glycosuria was also constant. The serum calcium varied between 10.3 and 11.5 mg. and the phosphorus between 0.4 and 1.3 mg. per hundred cubic centimeters. In both cases an exploration was made for parathyroid tumor, but none was found and the glands themselves appeared normal. Turnbull reported that sections of bone in the first case showed a great excess of osteoid tissue and moderately calcified bone. He considered that the diagnosis was osteoporosis and osteomalacia. Sections of bone in the second case showed no excess of osteoid tissue and considerable osteoporosis, but no evidence of osteitis fibrosa or osteomalacia. In both cases a decreased total output of calcium was noted, as well as an increase in the output of phosphorus in the urine. Hunter suggested that the kidneys failed to hold back phosphorus and calcium, just as they failed to hold back sugar, and that in consequence the plasma phosphorus content remained too low for normal formation of bone to take place.

It seems probable that in the cases reported by Michaëlis, Milkman, Leedham-Green and Golding, Hunter and Edeiken and Schneeberg the conditions were of similar origin, presenting as they did progressive softening of the bones, low serum phosphorus content, no evident renal disease and, in 4 cases, renal glycosuria. Therapy has so far failed to affect the condition.

Hunter's hypothesis that the kidney is at fault is supported by our findings. We would suggest, then, that there is a small group of cases in which osteoporosis is dependent on a defect of the renal tubules. The features of such a group are progressive softening of the bones, with or without fractures, unassociated with deficient dietary intake, signs of chronic nephritis or hyperparathyroidism, a normal serum calcium and a low serum phosphorus level, increased output of phosphorus and low excretion of calcium in the urine.

25. Hunter, D.: Studies in Calcium and Phosphorus Metabolism in Generalized Diseases of Bones, Proc. Roy. Soc. Med. **28**:1619, 1935.

The need, however, for further studies on excretion of phosphate in osteoporosis of obscure causation is evident. The low glucose threshold may or may not be part of the renal defect, but more cases must be studied before this question can be decided.

SUMMARY

In the case of a 39 year old man with progressive osteoporosis, laboratory and postmortem investigations suggested that a functional defect of the renal tubules led to a persistently low serum phosphorus content and that this was the cause of the osteoporosis. Six similar cases have been reported in the literature. Our case, in conjunction with these 6, offers support for Hunter's hypothesis that osteoporosis may on occasion be due to a renal defect unassociated with signs of chronic nephritis. The features of this group of cases are progressive osteoporosis, with or without fractures, unassociated with obvious dietary deficiencies, signs of chronic nephritis or hyperparathyroidism, in the presence of a normal serum calcium content, a low serum phosphorus content, an increased phosphorus level and a decreased calcium excretion in the urine, often associated with renal glycosuria.

Prof. W. H. Wynn gave us permission to investigate and publish the data on this case. Mr. Garfield Thomas, biochemist, and Mr. J. Parkes, assistant biochemist, Queen Elizabeth Hospital, and Miss J. Traught, biochemist to Dudley Road Hospital, made numerous biochemical investigations. Dr. J. F. Brailsford contributed advice on the interpretations of the roentgenograms, Dr. A. E. Chaplin carried out the postmortem examination and made the report and Dr. W. Whitelaw, pathologist to the Birmingham Municipal Hospitals, granted us permission to publish these data.

EARLY AMYLOID NEPHROSIS IN COMPLICATED TRAUMAS OF THE BONE SUSTAINED DURING WAR

SAMUEL D. REISELMAN, M.D.
Professor of Therapeutics, Kharkov Medical Institute
KHARKOV, UNION OF SOVIET SOCIALIST REPUBLICS

THE PROBLEM of the interrelation of the osseous and renal changes has long been known. More than twenty years prior to the writing of this paper, Barber [1] described a retardation of growth in children who have suffered for a long time from chronic nephritis or hydronephrotic atrophy of the kidneys. This retardation of growth may be associated with deformities of the bone and has been called "renal dwarfism" by the aforementioned author. Other authors use the terms renal infantilism, renal nanism or renal rickets for this disease (Shipley [2] and his co-workers, Lathrop,[2] Schoenthal and Burpee [3] and others). Investigations of Parsons [2] indicate that in renal infantilism there is a considerably extended rarefaction of the bones, observed roentgenologically. Fishberg [4] considered the term "renal rickets" a misnomer, as histologic osseous changes in this disease are much more closely related to those of hyperparathyroidism than to those of rickets. Moreover, his observations and those of Karelitz and Kolomoyzeff [5] and others would indicate that antirachitic therapy in these cases has little or no effect.

While the pathogenesis of the osseous changes in renal infantilism has not been altogether elucidated, Fishberg [4] has stated the belief, however, that there can be little doubt that this osteodystrophy is the result of the disturbances in mineral metabolism, produced by renal insufficiency. Most probably this metabolic disturbance is closely connected with disturbances in calcium metabolism, as it was experimentally

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1. Barber, H.: The Bone Deformities of Renal Dwarfism, Lancet **1**:18 (Jan. 3) 1920.

2. Cited by Fishberg.[4]

3. Schoenthal, L., and Burpee, C.: Renal Rickets, Am. J. Dis. Child. **39**:517-528 (March) 1930.

4. Fishberg, A. M.: Hypertension and Nephritis, London, Baillière, Tindall & Cox, 1934.

5. Karelitz, S., and Kolomoyzeff, H.: Renal Dwarfism and Rickets, Am. J. Dis. Child. **44**:542-555 (Sept.) 1932.

demonstrated by Pappenheimer,[6] and is similar to the one present in primary parathyroid adenoma (Albright and others [7] and Shelling and Remsen [8]). It appears evident that long-standing impairment of renal function leads to enlargement of the parathyroid apparatus.

Thus Pappenheimer and Wilens [9] found that the weight of the parathyroids in patients with renal insufficiency averages more than 50 per cent greater than that of the parathyroids in controls. Highman and Hamilton [10] demonstrated experimentally on rats that there is a hyperfunction of the parathyroid glands in chronic renal disease, as measured by the effect of a patient's blood on the calcium content of a rat's blood. Albright and his associates [7] described similar alterations of the parathyroid apparatus in human beings with chronic nephritis. It is probable that the stimulus to the function of the parathyroids is retention of phosphate in renal insufficiency.

Rusakov,[11] one of the first in the Soviet literature to call attention to the interrelation existing between the kidneys and the osseous system, expressed the opinion that the osseous changes in renal insufficiency are seldom noticed only because they are not looked for. He suggested that every case of long-standing renal insufficiency entails hyperplasia of the parathyroid glands, with consequent development of the osseous changes of the type of osteodystrophy fibrosa, which he termed nephrotic osteopathies. He referred in these cases to the secondary hyperparathyroidism and not the primary one, i. e., Recklinghausen's disease. The latter is often associated with calcification of the renal parenchyma, with impairment of its function, or with the formation of calculi in the renal pelvis. Rusakov referred to the investigations of American authors who had found impairment of renal function with formation of calculi in 50 to 75 per cent of the instances of Recklinghausen's disease. He described 4 cases of parathyroid dystrophy, in 3 of which he observed changes in the renal parenchyma of the type of calcified metastasis, with impairment of its function, and in 1 the formation of calculi, with subsequent death of the patient.

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6. Pappenheimer, A. M.: Effect of Experimental Reduction of Kidney Substance upon Parathyroid Glands and Skeletal Tissue, J. Exper. Med. **64**:965-980 (Dec.) 1936.

7. Albright, F.; Drake, T. G., and Sulkowitch, H. W.: Renal Osteitis Fibrosa Cystica, Bull. Johns Hopkins Hosp. **60**:377-399 (June) 1937.

8. Shelling, D. H., and Remsen, D.: Renal Rickets, Bull. Johns Hopkins Hosp. **57**:158-181 (Sept.) 1935.

9. Pappenheimer, A. M., and Wilens, S. L.: Enlargement of Parathyroid Glands in Renal Disease, Am. J. Path. **11**:73-91 (Jan.) 1935.

10. Highman, W. J., Jr., and Hamilton, B.: Hyperparathyroidism in Kidney Disease, J. Clin. Investigation **16**:103-105 (Jan.) 1937.

11. Rusakov, A. W.: Osteogenic Nephropathies and Nephrogenic Osteopathies, Klin. med. (no. 1) **17**:46-54, 1939; (no. 2-3) **17**:41-52, 1939.

As yet, however, it must be admitted that the pathogenesis of the formation of calculi is obscure, and there appears to be no reason for the belief that it is due only to the disturbances in calcium metabolism. Nevertheless, the investigations of a number of authors would indicate that the formation of stones in the kidneys is often observed in various neoplasms and inflammatory processes in bones, involving extensive destruction of bone and invasion of the blood by the products of altered calcium metabolism.

Moreover, if it is remembered that the disturbances in the vitamin balance of the organism, particularly a vitamin A deficiency (Gasparjan and Ovtchinnikov [12] and Osborne and Mandel [13]), as well as the changes in the equilibrium of the vegetative nervous system and the variations in the urinary and blood colloids also play an important role in the pathogenesis of the formation of stones, it will be easy to understand that the various injuries to the bone occurring under wartime conditions may lead to a comparatively rapid development of renal lithiasis. At the present time, similar conditions among the wounded participants of World War II have been already described. My associates and I have also observed 2 such cases of abundant formation of stones in kidneys, undoubtedly associated with injuries of bones sustained during the war.

In a discussion of the interrelation of the pathologic processes in the bones and in the kidneys it is necessary to mention also the myeloma, mostly a multiple osseous neoplasm described by Rustizky and Kahler and called therefore the Rustizky-Kahler disease. This disease favors the development in the bones of a neoplastic tissue of a specific character, followed by a considerable destruction of the osseous substance. Moreover, the urine and blood reveal the presence of albumose under the form of the so-called Bence Jones protein. Numerous original hyaline casts are to be found in the kidneys, giving an intensive color reaction of amyloid with the use of congo red. As a matter of fact, this last circumstance gave some authors the ground to speak of a chemical relationship between amyloid and the Bence Jones albumose.

Rustizky-Kahler disease may lead to a complete occlusion of the nephrons by the Bence Jones albumose and consequently to oliguria and anuria, to the onset of renal insufficiency and finally to uremia. While edema is a common feature of the cachectic condition in patients with other malignant neoplasms, it is characteristic, according to Fishberg [4] and other authors, that in this form of neoplasm it is not observed.

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12. Gasparjan, A., and Ovtchinnikov, N.: Zur Frage der Steinbildung im Organismus (Avitaminose und Steinbildung), Ztschr. f. urol. Chir. **30**:365-374, 1930.

13. Cited by Volhard, F., and Suter, F.: Nieren und ableitende Harnwege, in Mohr, L., and Staehelin, R.: Handbuch der inneren Medizin, Berlin, Julius Springer, 1931, vol. 6, pt. 2, p. 1913.

Rusakov [11] considered that the Bence Jones albumose is the result of the impairment of the intraosseous intercellular protein metabolism and called the entire process in the kidneys osteogenous nephropathy.

There exists, however, still another, more intimate, relationship between the osseous system and the kidneys, a relationship in which the kidneys act as a conjugate but unique organ and as a system connected by the community of humoral and nervous relations with the whole organism. I refer to amyloid nephrosis, a disease whose position in the scheme of the classification of renal diseases offers some difficulties. From the purely morphologic standpoint, the amyloid kidney is, perhaps, most closely related to arteriosclerotic diseases of the kidneys, for the lesions are primarily degenerative changes in the renal vessels. But, clinically, except in unusual instances of amyloid contracted kidney, the principal features of the disease seem to consist in the degenerative changes in the tubular epithelium of the kidneys and not in the circulatory changes in the glomeruli.

It is still considered an established fact that amyloid nephrosis is closely associated pathogenetically with the presence of long-standing chronic diseases accompanied with cachexia and, more particularly, with pulmonary and osteoarthritic tuberculosis and long-standing suppurations, such as those in empyema, bronchiectasis, pulmonary abscess, osteomyelitis and other conditions. However, the question of the necessity in the presence of a long-standing suppurative or infectious process for the development of amyloid nephrosis requires reconsideration. A series of findings of older authors have been recorded who have proved experimentally the possibility of an extremely early development of amyloidosis and amyloid nephrosis. Thus Krawkow in 1896 found amyloid after eleven days of experimentally produced suppuration in rabbits.

Birch-Hirschfeld in 1892 observed the development of amyloidosis under similar conditions within six weeks. An American investigator, Dickinson, found amyloidosis in a patient three weeks after a compound fracture, and Rosenblatt,[14] also an American, observed the development of amyloidosis among one fifth of his tuberculous patients within less than two years from the onset of tuberculosis and in some patients even within not later than six months thereafter. Lichtwitz [15] described a case of the development of amyloid nephrosis and amyloidosis of the spleen in a patient who died of pneumonia within three weeks.

These facts are not only of diagnostic but also of prognostic importance. Usually in patients in the early stages of the disease amyloid

14. Rosenblatt, M. B.: Recovery from Generalized Amyloidosis Secondary to Pulmonary Tuberculosis, Arch. Int. Med. **57**:562-565 (March) 1936.

15. Lichtwitz, L.: Die Praxis der Nierenkrankheiten, Berlin, Julius Springer, 1925.

nephrosis often figures in the hospitals under the diagnosis of "decompensation of cardiac function" or "nephronephritis" and in the later stages, with the onset of renal insufficiency, as chronic nephritis. Naturally this may lead to defective treatment. On the other hand, a vigorous treatment effectively pursued to combat the basic pathogenetic source of the disease may not only save the patient from premature death but lead to full recovery in cases in which the process in the kidneys is not yet in the incurable stage. A number of cures thus attained have been reported (Waldenström,[16] Fishberg,[4] Reimann [17] and others) which took place once the primary cause of amyloid nephrosis had been removed. We have also seen such an instance of complete recovery from amyloid nephrosis (at least the clinical course did not reveal the presence of amyloid during a two year period) in a patient with tuberculous osteomyelitis of the hip after the amputation of the extremity. That amyloidosis can regress once the cause has been removed is known also from the experiments of Kuczynski [18] in 1922.

Because of the view that amyloid nephrosis requires a prolonged period for its development, this disease may not be always recognized in time, and the possibility of its effective treatment may thus be neglected.

Moreover, amyloid nephrosis is often not recognized because of the erroneous view that this process is accompanied usually with pronounced albuminuria, as in chronic and lipid nephrosis.

Despite this extended point of view, it should be borne in mind that albuminuria in the presence of amyloid nephrosis is variable and at times may practically disappear. The number of formed elements present in the urinary sediment in amyloid nephrosis is extremely low, much lower than that in equally severe albuminuria in other forms of renal disease.

Edema is an exceedingly common symptom of amyloid nephrosis, and as a rule the lower extremities are first and most affected. The latter fact presents another occasion to attribute the origin of edema to the presence of a nonexisting or hardly onsetting cardiac weakness. Ascites is not uncommon, and sometimes there may be ascites in the absence of anasarca. Hydrothorax is extremely rare.

If it is further added that in amyloid nephrosis diarrhea may be present as an evidence of intestinal amyloidosis, it will be easy to

16. Waldenström, H.: Formation and Disappearance of Amyloid in Man, Acta chir. Scandinav. **63**:479-530, 1928.

17. Reimann, H. A.: Recovery from Amyloidosis, J. A. M. A. **104**:1070-1071 (March 30) 1935.

18. Kuczynski, M. H.: Neue Beiträge zur Lehre vom Amyloid, Klin. Wchnschr. **2**:727-730, 1923.

understand why these patients are often treated for avitaminosis, chronic enterocolitis, dysentery or alimentary dystrophy.

It would seem that an accurate analysis of the diagnostic particularities in amyloid nephrosis will show that its frequency among wounded patients with complicated traumas of the bone sustained during the war may be much higher than it is supposed. At least after special attention had been called to this problem we had the occasion to observe several such patients.

As an illustration short summaries of cases of some of such patients are submitted.

REPORT OF CASES

CASE 1.—D. E., a private aged 33, was wounded on Aug. 1, 1942 by a mine fragment in the left humerus. He was admitted to the evacuating hospital with a plaster cast applied, which was left undisturbed. Pronounced edema of the lower extremities and the face was present. Urinalysis (made first on August 22) revealed up to 3 Gm. of albumin per hundred cubic centimeters, 2 or 3 hyaline casts in the sediment and 3 to 5 alkalinized red blood cells microscopically. There was diarrhea without mucous or bloody stools. The patient died on August 26 with symptoms of cardiac insufficiency.

Clinical Diagnosis.—There was a gunshot fracture of the left humeral bone, with a suppurative process, and wounds involving the soft tissue of the left thigh. Nephritis (with possibly a renal abscess) and colitis were present.

Autopsy.—Autopsy was performed on August 27. The spleen was sharply enlarged (weight 500 Gm.), extremely hard and of elastic consistency, and it broke on section. On scraping, pulp was absent. The kidneys were enlarged, weighing together 525 Gm., and had a hard surface; the tissue appeared sharply pale, waxy and hard and was marked by the appearance of slightly yellowish spots on the surface. Application of strong solution of iodine, U. S. P., produced brownish small dots and strips (a reaction positive for amyloid). The mucosa of the pelvis, ureter and urinary bladder was pale.

Anatomic Diagnosis.—A gunshot fracture, by fragment, of the left humeral bone, with consequent osteomyelitis and suppuration of the soft tissues in the region of the fracture, was present. There were two fistulous communications in the skin of the left humerus in the region of the wound. Also found were amyloid nephrosis, amyloidosis of the spleen (which was lardaceous) and fresh serofibrinous ascitic peritonitis.

This was a case of sharply pronounced amyloid nephritis which developed within two or three weeks after a gunshot wound, with consequent osteomyelitis. The most careful research during autopsy did not reveal any other cause for the development of the disease.

CASE 2.—I. D., a private aged 40, was wounded on Feb. 23, 1942 in the region of the left knee joint. Arthrotomy was performed on March 6. During the course of the operation there was a copious discharge of pus. On March 25 the patient was evacuated to the base hospital, with complaints of great pains in the left leg. The discharge of pus from the wound was still copious. On April 14 edema made its appearance, occurring first in the lower extremities and then in the whole body. Beginning on April 23 the patient had frequent watery stools. On May 4 the possibility of amyloid nephrosis was first suspected. The urine

contained from 1 to 6 Gm. and more of albumin per hundred cubic centimeters and a few formed elements in the sediment. The patient showed growing general weakness, and he died on April 15 in the last degree of cachexia.

Autopsy.—Autopsy revealed osteomyelitis of the left femur, amyloid nephrosis and amyloidosis of the spleen, liver and bowel.

In this case, as in the previous one, besides osteomyelitis, autopsy did not reveal any other cause for the development of amyloid nephrosis. The disease developed probably within six or seven weeks after the injury. Possibly an early radical operation could have saved the patient.

CASE 3.—Y. K., a private aged 27, sustained an incomplete wound by shell fragment in the region of the third thoracic vertebra on June 11, 1942. There were signs of compression of the spinal cord. On June 13 laminectomy was performed, with the application of a fixating splint. From July 30 there appeared small bed sores, measuring 2 by 1 and 3 by 1 cm., in the region of both trochanters. These increased and extended, and there appeared a copious purulent discharge. On July 20 the patient was evacuated to the base hospital. On July 27 there was 0.66 Gm. of albumin per hundred cubic centimeters in the urine, with no formed elements; later the albumin disappeared from the urine. On August 20 —two months and nine days after injury—edema of the feet and then of the whole body appeared. From August 28 there was diarrhea, with growing cachexia. Albumin was present, from 0.33 to 1.65 Gm. per hundred cubic centimeters; no casts were seen. The patient died on September 15 with pronounced cachexia.

Clinical Diagnosis.—An incomplete wound of the spinal column in the region of the third thoracic vertebra was seen. There were also paraplegia of the lower extremities, paralysis of the pelvic organs, amyloid nephrosis and bed sores.

Autopsy.—Autopsy performed on September 7, revealed the liver to be large and hard, with a greasy luster. The kidneys were large and white. There was a positive reaction to strong solution of iodine, U. S. P. At the level of the fourth and fifth thoracic vertebrae there was an opening through the spine and ribs into the right pleural space.

Diagnosis.—The diagnosis of an incomplete wound of the spine, with consequent myelitis was made. There were purulent pleurisy and pneumonia, with an abscess, involving the left side. There was also amyloidosis of the internal organs along with amyloid nephrosis.

In this case amyloidosis developed within three months after the patient's injury. The possible causative factor seems not to be trauma of the bone directly but processes associated with this condition (purulent pleurisy involving the left side, abscess of the lung and bed sores).

CASE 4.—I. M., a private aged 32, was wounded on June 13 by mine fragments in the lumbar region, both buttocks and feet. It was recorded on July 4 in the front hospital that he had a wound measuring 3 by 1 cm. in the region of the "lumbar vertebrae," with copious purulent discharge. On July 8, less than one month after injury, the patient, because of general edema and poor general condition and the presence of up to 6 Gm. of albumin per hundred cubic centimeters of urine, was evacuated to the base therapeutic hospital. On July 9 the blood pressure was 110 systolic and 55 diastolic. Albumin in the urine varied from 2.31 and 2.64 to 4.29 Gm. per hundred cubic centimeters. A small quantity of hyaline casts was present in the sediment. On July 17 the patient looked

extremely pale and weak and there was considerable edema of the lower extremities and the scrotum. From August 4 there were diarrhea and cachexia. The patient died on August 12.

Clinical Diagnosis.—Osteomyelitis of the right iliac bone was diagnosed, with nephritis and enterocolitis.

Autopsy.—At autopsy the kidneys were enlarged, hard and light yellow. The spleen was hard and lardaceous.

Anatomic Diagnosis.—The anatomic diagnosis was osteomyelitis of the left iliac bone after a gunshot wound, with amyloid nephrosis and amyloidosis of the spleen and bowel.

CASE 5.—I. M., a private aged 36, was wounded on Feb. 12, 1942 by a mine fragment in the left thigh. On February 16 there was a copious discharge of pus from the wound. The patient was recorded as having osteomyelitis of the left femoral bone. On April 22, two months and ten days after injury, the onset of general edema occurred. The blood pressure was 105 systolic and 70 diastolic. Urinalysis revealed 0.33 Gm. of albumin per hundred cubic centimeters and hyaline casts in the sediment.

Diagnosis.—Avitaminosis was diagnosed. In spite of an adequate diet the edema lasted. Purulent discharge from the wound continued. In the urine there were varied amounts of albumin—from 0.33 to 1.28 Gm. per hundred cubic centimeters. The blood pressure was not high. On May 25 amputation was performed through the lower end of the left femur. On June 16 diarrhea developed; the edema diminished. The patient died on June 22.

Clinical Diagnosis.—The clinical diagnosis was amputation of the left femur due to traumatic osteomyelitis, with amyloid nephrosis.

Autopsy.—Autopsy was performed on June 23. The kidneys were enlarged, weighing together 582 Gm., and of hard consistency, revealing a light yellow, waxy tissue. There was a positive reaction to strong solution of iodine, U.S.P. The spleen was hard, fragile and lardaceous.

Anatomic Diagnosis.—The anatomic diagnosis was amyloid nephrosis, with amyloidosis of the spleen.

As seen from the foregoing report, in this case the amyloid nephrosis developed within four months after injury. The amputation of the wounded extremity, executed three and a half months thereafter, did not stop the progress of amyloidosis, probably being too delayed.

We have at our disposal 28 such cases as described here in which the diagnosis of early amyloid nephrosis and amyloidosis of various internal organs (spleen, liver or bowel) was established during autopsy (or partially clinically). All of them are more or less similar as to the course of the disease. We observed some patients who had early amyloid nephrosis which developed in direct connection with the complication of trauma of the bone sustained in the war but in whom the process was considerably less acute. Owing to the improvement in the basic traumatic process, all the patients were discharged from hospitals in a more or less satisfactory condition. However, the osteomyelitic process, as well as the process in the kidneys, is probably only in an inactive stage. For these reasons, the possibility of further

progress of amyloidosis and amyloid nephrosis resulting in the amyloid contracted kidney, with all its severe consequences, is always awaiting these patients. To our regret, due to present conditions, further observation of these patients is rather complicated.

In view of the fact that the diagnosis of amyloid nephrosis, especially in its early stages, presents some difficulties and may always provoke some doubt, especially if it is not confirmed by the Bennhold reaction with the solution of congo red (which test we could not use because of technical circumstances), I have described only the cases in which the diagnosis was confirmed by autopsy. Evidence has been accumulated which indicates that often cases of amyloid nephrosis have been recorded in which not only clinically but even at necropsy it was impossible to establish the primary cause for the development of the process. The suppurative process may be so insignificant and so deeply hidden in various tissues that it may easily escape the attention of the prosecutor even during the most careful search. Probably in our cases too the cause for the development of the amyloid process was not the complicated trauma suffered in the war but some other long-standing infectious suppurative process which was present in the organism of the patients long before the trauma.

It would appear, however, that such an admission is extremely artificial. It is hardly admissible that all our patients could have such a long-standing process without its being revealed clinically or at necropsy. Perhaps such a supposition is apt to be true in regard to some of our patients, but it cannot be extended to include all of them. Too clear in our cases is the association of the process with the trauma, and too often was there a development of both processes to deny their relationship.

Unexpected and totally inconsistent with our usual observations is the extremely early development of amyloid nephrosis which occurred after the trauma in our cases. Thus in our first case the amyloid nephrosis developed within two or three weeks after the injury and in the other cases within two or three months. The latter term, sufficiently early too in comparison with the usual occurrence in our cases, we observed in the case of a wounded soldier, in whom proved amyloid nephrosis developed eight months after the injury.

However unexpected this fact may be, it must not astonish physicians. Conditions in wartime may cause exceedingly original courses and highly varied pictures of the usual and well known pathologic changes. This does not refer only to the problem which is of interest to us but to the varied pathologic pictures, the original forms of which, under the conditions occurring in wartime, every more or less observing clinician may note at the present time. Malaria, pneumonia, pneumosclerosis and other related conditions assume at the present time

such original forms that their diagnosis offers some difficulties. In particular, in connection with the renal pathologic changes, the so-called war (trench) nephritis is worthy of mention. Its course differs so considerably from the acute diffuse nephritis occurring in peacetime that a number of authors have been inclined to consider it a special nosologic variety, even though it does not differ either pathogenetically or clinically from the latter. It is easy to assume, therefore, that in the organism exposed for a long time to the hardships of life in the open air, frequent cold (and perhaps light infections), altered diet and strong psychic trauma the process of the development of amyloid nephrosis may progress more swiftly.

Such conditions as described here are rather rare; however, they are more frequent than it may be supposed. The interest in them is not only of a theoretic character, consisting in the mere possibility of such an early development of amyloid nephrosis. A timely diagnosis of such impairments of renal function in wounded persons should call for greater activity on the part of surgeons, including more energetic and radical surgical intervention. This in its turn may be lifesaving in such cases or may preserve the patients from early painful invaliding and finally from premature death.

69 Sumskaja Street.

EXCRETION OF UROBILINOGEN IN THE URINE IN INFECTIOUS HEPATITIS

Serial Studies

HOWARD A. LINDBERG, M.D.
AND
GEORGE V. LeROY, M.D.
CHICAGO

ALTHOUGH it has been known for many years that the Ehrlich reaction for urobilinogen in the urine and feces is a sensitive test of hepatic dysfunction,[1] not until recently has there been a simple quantitative method for its determination. In 1944 Watson and others described a simple quantitative method for measuring the urinary excretion of urobilinogen.

During the active phases of the Pacific campaign, in a hospital in Guadalcanal, we had the opportunity of comparing this test with several other sensitive tests of hepatic function in the study of 120 cases of infectious hepatitis. We attempted to determine whether or not this test could be used in assisting clinical judgment to decide when convalescence should be terminated. Most of our patients were seen after jaundice had developed and were followed during the period of convalescence to complete recovery or to the point at which it was evident that their convalescence would be considerably prolonged and that the need for further rest required their evacuation to the zone of the interior.

One of the main purposes of tests of hepatic function in cases of hepatitis is to determine when convalescence has progressed far enough so that there is the minimum possibility of relapse after a patient has resumed his daily activities. Certain tests of hepatic function are important also in the estimation of residual hepatic damage many months after the acute disease has subsided. They may also be used in group survey studies during an epidemic of infectious hepatitis to detect patients who are without icterus but who do have latent disease. Such studies may reveal subclinical forms of disease, which, if undiscovered, might progress and leave permanent hepatic damage.[2]

From the Department of Medicine, Northwestern University Medical School.

Read before the Midwest Section, American Federation for Clinical Research, Chicago, Oct. 31, 1946.

1. Wallace, G. B., and Diamond, J. S.: Significance of Urobilinogen of the Urine as a Test of Liver Function, Arch. Int. Med. **35**:698-725 (June) 1925.

2. Hallock, P., and Head, D. P.: Simple Laboratory Test as Aid in Recognizing Early Hepatitis, Bull. U. S. Army M. Dept. **5**:236-242 (Feb.) 1946.

As long as the patient with acute infectious hepatitis is jaundiced and has a palpable, tender liver, there is no question of his status as a bed patient or of the deficiency of his hepatic function. Therefore, gross tests of hepatic function, such as dextrose and galactose tolerance tests and tests for hippuric acid synthesis and abnormal cholesterol levels, which may reveal abnormality during the acute phase, usually are not helpful in the ultimate management of the patient. Abnormalities in the alkaline serum phosphatase activity and in the amount of cholesterol esters, total protein and globulin in the plasma have their greatest prognostic value early in the course of the illness and are much less important late in convalescence or in chronic hepatitis. More sensitive tests of hepatic function, such as Hanger's cephalin-cholesterol flocculation test, the thymol turbidity test, the one minute direct van den Bergh reaction and the thirty minute sulfobromophthalein excretion test, have been fairly reliable guides to recovery.[3] On many occasions, however, relapses have occurred after the reactions to these tests have become normal and after the patient has apparently recovered clinically, in some instances having been ambulatory for seven to ten days or longer. Thus a test which may aid in the detection of latent or incompletely cured hepatitis is greatly desired. To this end, the two hour quantitative excretion of urobilinogen has been observed during the convalescence of 120 patients with infectious hepatitis.

METHOD

The technic of the Watson test for urobilinogen in the urine depends on the comparison of the color developed in the urine by the Ehrlich diazo reagent with that developed by a stock solution of a standard dye (pontacyl fast pink, E. K.).[4] Estimations can be made in a simple comparator block or in the Evelyn or some other photoelectric colorimeter. In normal circumstances the maximum rate of excretion of urobilinogen occurs between 2 and 4 in the afternoon and probably does not exceed a total of 1.0 to 1.5 Ehrlich units for the two hour collection period. The usual normal range in our experience varied from 0.6 to 0.8 unit for the two hour period. In hepatic dysfunction of the sort caused by infectious hepatitis but without complete biliary obstruction, more than 1.0 Ehrlich unit is excreted during this same period. The normal urinary excretion in twenty-four hours is usually less than 5.0 Ehrlich units.

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3. Barker, M. H., and Capps, R. H.: Acute Infectious Hepatitis in the Mediterranean Theater Including Acute Hepatitis Without Jaundice, J. A. M. A. **128**:997-1003 (Aug. 4) 1945. Barker, M. H., and Capps, R. H.: Chronic Infectious Hepatitis in the Mediterranean Theater, J. A. M. A. **129**:653-659 (Nov. 3) 1945.

4. Schwartz, S.; Sborov, V., and Watson, C. J.: The Quantitative Determination of Urobilinogen by Means of the Evelyn Photometer Colorimeter, Am. J. Clin. Path. **14**:598-603 (Dec.) 1944. Watson, C. J.; Schwartz, S.; Sborov, V., and Bertie, E.: A Simple Method for Quantitative Recording of the Ehrlich Reaction as Carried Out with Urine and Feces, Am. J. Clin. Path. **14**:605-615 (Dec.) 1944.

During the course of this study on hospitalized patients with infectious hepatitis, we made a control series of urobilinogen excretion tests on a comparable group of young men, who were hospitalized in the surgical wards of the hospital. The test was performed between 2 and 4 p. m. on 56 patients. In 52 patients the results were normal. Four had excretions of urobilinogen in the urine of over 1.0 Ehrlich unit in two hours. The values were 1.2, 1.4, 1.45 and 1.5 Ehrlich units respectively. We did not have an opportunity to perform serial studies or other tests of hepatic function on these patients. In the 52 cases in which the values were less than 1.0 Ehrlich unit, the results ranged from 0.4 to 0.8 unit. Five patients with acute malaria and enlargement of the liver were tested. They excreted normal amounts of urobilinogen in the urine during the first five days of the disease, whereas 3 patients with amebic hepatitis had excretion values of more than 5.0 Ehrlich units in a two hour period. Studies of the twenty-four hour excretion of urobilinogen in the urine were performed on 5 normal controls. All 5 excreted less than 5.0 Ehrlich units in twenty-four hours.

RESULTS

The results of our studies will be presented in two parts: first, a report of the usefulness of serial determinations of the two hour excretion of urobilinogen in the urine in the management of patients with infectious hepatitis; second, a comparison of this test with other standard tests of hepatic function in a group of patients with acute infectious hepatitis. Even though our purpose in this present study was to compare the Watson two hour test of urobilinogen excretion with other tests, we are fully cognizant of the fact that no single estimation of hepatic function will measure over-all hepatic damage and that an evaluation of many tests is necessary. It is important that serial tests of hepatic function be done during the course of an acute infectious process of the liver. This was found to be particularly true of the Watson two hour test.

Part 1.—Tests for excretion of urobilinogen in the urine were done on each patient with infectious hepatitis at least every other day during the convalescent period, and not until three to five normal values were obtained over a seven to ten day period was convalescence considered to be completed. In doing serial studies, we noted that during the course of the illness and particularly during the convalescent period there were wide fluctuations in the amount of urobilinogen excreted in the urine and that unless the tests were performed at least every other day and interpreted for the individual patient the occasional test or spot check might give misleading normal values. Often these values were normal during the first two or three weeks of illness, until the icteric index reached the maximum level, becoming abnormal only after the icteric index began to decline (fig. 1 *A* and *B*). During convalescence there would be wide fluctuation, until the patient recovered, at which time the excretion of urobilinogen in the urine leveled off at normal values (fig. 1*C*). On other occasions there would be a rather close correlation

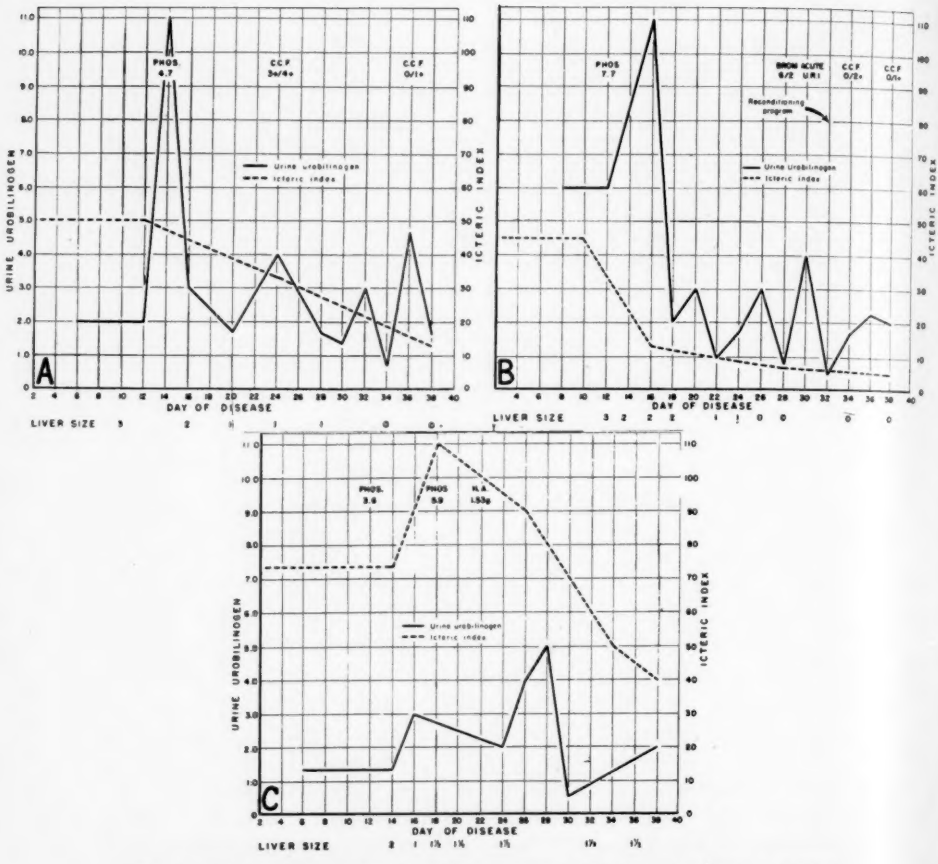

Fig. 1.—*A*, chart of a patient jaundiced for ten days before there was a decided rise in excretion of urobilinogen in the urine. After the icterus had begun to decrease, there were wide fluctuations in the amount of urobilinogen excreted, with some normal values occurring. Excretion was still abnormal after cephalin flocculation had become normal. *Phos.* indicates blood phosphatase; *Brom.*, excretion of sulfobromophthalein (thirty minute and sixty minute readings), and *C.C.F.*, cephalin-cholesterol flocculation (twenty-four to forty-eight hour reading). *B*, curve, similar to that in *A*, showing wide fluctuations in daily excretions. Abnormal amounts of urobilinogen in the urine were still being excreted after values in other tests of hepatic function had become normal. Note definite increase in values for urobilinogen as a result of an acute infection of the upper respiratory tract and early ambulation during the course of recovery. *C*, graph illustrates pronounced fluctuation of excretion of urobilinogen in the urine during active phases of acute hepatitis, even as the icteric index was approaching normal. Note that the patient had been jaundiced for two weeks before there was any striking increase in excretion of urobilinogen.

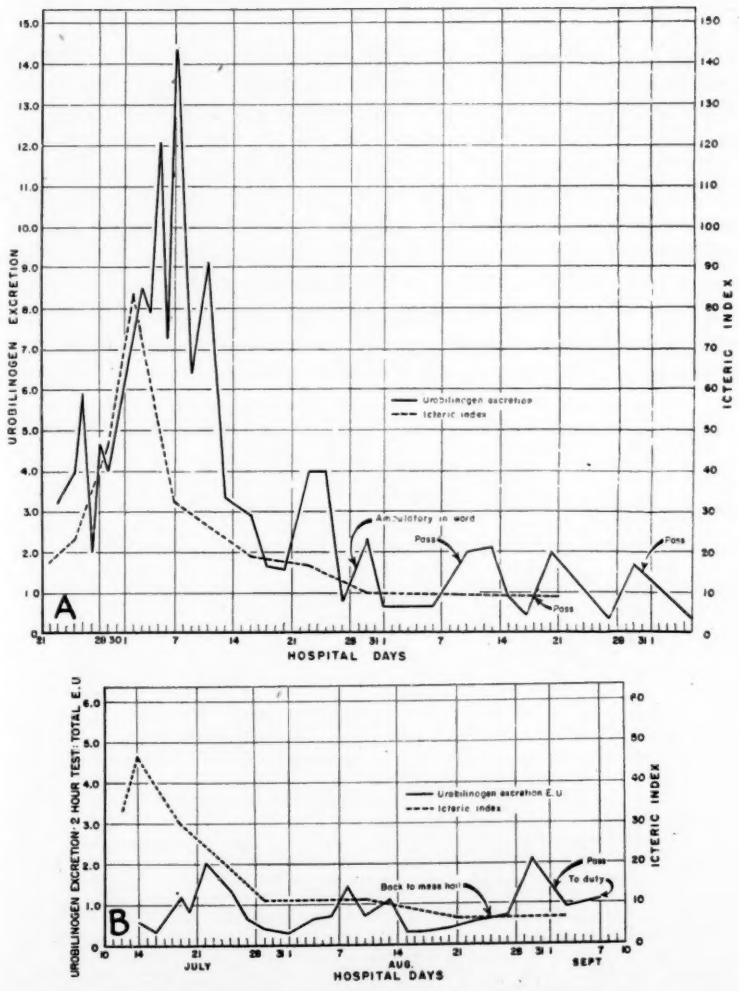

Fig. 2.—*A*, graph shows increase in excretion of urobilinogen in the urine corresponding to increase in values for icteric index as the peak of the illness is approached. After the icteric index begins to fall rapidly and reaches a normal level during the third week of the illness, there is a delay of fourteen days before the values for urobilinogen begin to approach normal. After the level of urobilinogen had become essentially normal, serial studies for urobilinogen in the urine revealed abnormal levels for thirty additional days. This was partially due to the effect of the patient's becoming ambulatory too early. The graph also illustrates the importance of serial studies of excretion of urobilinogen in the urine in an individual patient. The occasional normal levels found during the convalescent period may be misleading unless serial studies have been carried out. *B*, after levels of icteric index and excretion of urobilinogen had been normal for fourteen days, there was an immediate response in excretion of urobilinogen, but not in the icteric index, when the patient became ambulatory. One more week of rest was required before the level of urobilinogen became normal.

between the rise of the icteric index and the increase of excretion of urobilinogen (fig. 2). In most cases it was found that after the icteric index returned to normal and remained so the level of urobilinogen excretion would continue to fluctuate for two or three more weeks, depending on the patient's activity (fig. 2). After the values obtained in all other tests of hepatic function that were used, including the icteric index test, had become normal and the liver had not been palpable or tender for at least two weeks, the values for excretion of urobilinogen had a tendency to remain high for from several days to two weeks (fig. 3). In some cases in which clinical recovery seemed to be prompt and the icteric index dropped rapidly, there was a rather close correlation between the return of the excretion of urobilinogen in the urine

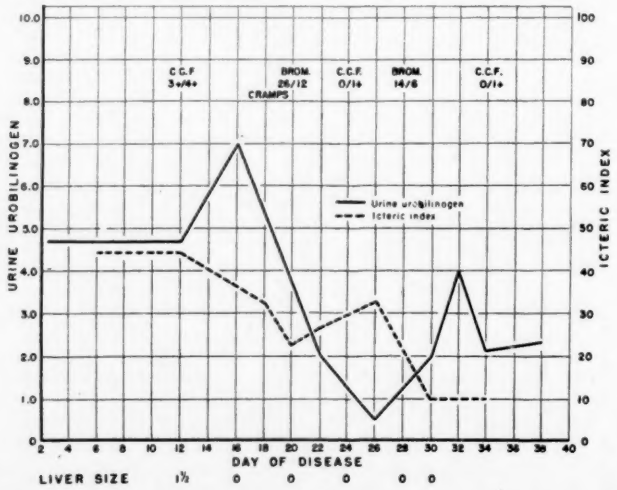

Fig. 3.—Graph illustrates the fact that values in all other tests of hepatic function had become normal and that the liver had been normal in size and nontender for at least two weeks while increased levels of urobilinogen in the urine were still present. Note the decided increase in excretion of urobilinogen, which occurred on a day in which the patient had an acute gastrointestinal upset, which was probably related to the hepatitis.

and the icteric index to normal, providing the patient did not become ambulatory too early (fig. 4). If he became active too early, the value for urobilinogen excretion would remain elevated, finally becoming normal after a two or three week period if convalescence continued and no relapses interfered (fig. 5).

Summary.—The graphs reveal that it was desirable in each individual case to test the excretion of urobilinogen in the urine daily and to follow these levels until they had become normal. Only in this way could we decide, after the patient appeared to be clinically well, whether con-

valescence was actually completed or whether there was a tendency to relapse with increased activity. The number studied is too small to permit drawing conclusions, but it was our impression that patients were less liable to relapse when activity was forbidden until the excretion of urobilinogen in the urine had been within normal limits for about one week. Further study is needed in this direction.

Part 2.—For the purpose of adequate presentation of data, our series of 120 cases were divided into three classes on the basis of the intensity of the icterus at the height of the disease, as follows: (*a*) mild—icteric index less than 20 units (54 cases), (*b*) moderate—icteric index from 21 to 50 units (53 cases), (*c*) severe—icteric index more than 51 units

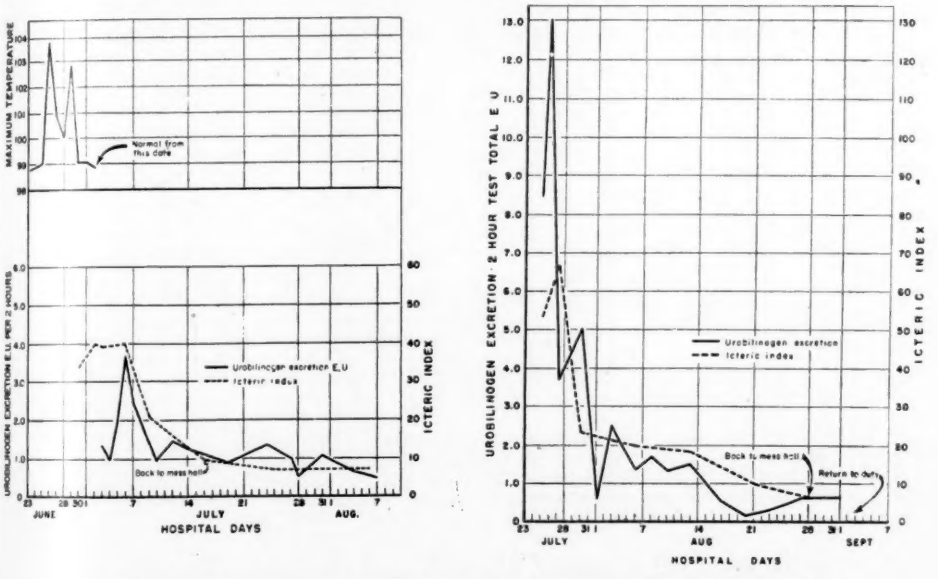

Fig. 4.—Graphs show the correlation between the fall of the icteric index and the rate of excretion of urobilinogen in the urine, with sustained normal levels in moderately ill patients with hepatitis who recovered rapidly without incident and who were kept in bed until recovery was complete.

(13 cases). In general, the classification agreed with the severity of the clinical symptoms.

In addition to the routine estimations of the icteric index, the following tests of hepatic function were performed on all patients for the purpose of comparison: (1) test for excretion of urobilinogen in the urine (two hour quantitative method of Watson), in which the normal value is 0.25 mg. (or 1 Ehrlich unit) or less for a two hour period, (2) a sulfobromophthalein retention test (using 5 mg. per kilogram of dye),

in which the normal value is 6 per cent or less retention after thirty minutes, (3) cephalin-cholesterol flocculation test (the twenty-four hour reading only is recorded in this report), in which the normal result is no flocculation and (4) test for activity of serum alkaline phosphatase, in which the normal value is less than 3.5 Bodansky units.

Plasma protein levels were determined many times, but they were not found to be significantly altered in all cases during the convalescent phases of the disease and for comparison purposes were not included in this report.

In table 1 are presented the results of tests performed while icterus was still evident. The values used in the calculation of each percentage were the most abnormal ones observed, and they may be assumed to represent the greatest deviation from normal encountered in indi-

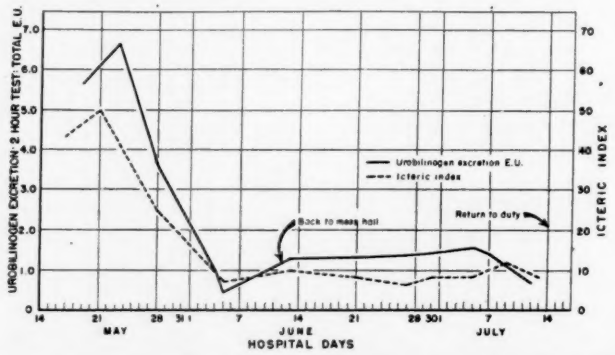

Fig. 5.—Increase in excretion of urobilinogen in the urine from normal to abnormal levels when the patient became ambulatory and remained so after the icteric index had become normal. Recovery was not complete until at least four weeks after the patient had become ambulatory and the icteric index had reached normal levels.

vidual cases. It is possible, of course, that had serial determinations of each test been performed the incidence of normal results might have been less. It has been common experience that many of the functional tests may not indicate abnormalities of function except as a result of extreme damage. Accordingly, the data are summarized to show in what percentage of each class normal values were obtained from a given test while icterus was still evident. Obviously, tests which give normal results at a time when the liver is certainly diseased have a limited value at best.

In table 2 the data are presented in a different manner. Many tests were performed after jaundice had disappeared, in an attempt to estimate the "residual hepatic damage" referred to previously. In this summary is given the percentage of cases in which each of the tests yielded

abnormal values during the first week or two after the icteric index became normal. It is a fair assumption from clinical experience that hepatic damage persists in patients with infectious hepatitis for some time after the jaundice disappears. A test which will indicate the existence of such damage is obviously of value, and its relative usefulness can be found by this method. After the icteric index became normal the tests outlined in table 2 continued to yield abnormal values.

TABLE 1.—*Results of Tests of Hepatic Function Performed While Icterus Was Present*

Normal values for excretion of urobilinogen in the urine were found in:
(1) 20% of 35 cases of mild hepatitis
(2) 17% of 41 cases of moderate hepatitis
(3) 0% of 12 cases of severe hepatitis
(4) 16% of all cases

Normal values for retention of sulfobromophthalein were found in:
(1) 57% of 33 cases of mild hepatitis
(2) 25% of 20 cases of moderate hepatitis
(3) 20% of 5 cases of severe hepatitis
(4) 43% of all cases

Normal values for cephalin-cholesterol flocculation were found in:
(1) 60% of 17 cases of mild hepatitis
(2) 40% of 22 cases of moderate hepatitis
(3) 16% of 6 cases of severe hepatitis
(4) 45% of all cases

Normal values for activity of serum alkaline phosphatase were found in:
(1) 72% of 7 cases of mild hepatitis
(2) 35% of 17 cases of moderate hepatitis
(3) 25% of 8 cases of severe hepatitis
(4) 44% of all cases

TABLE 2.—*Hepatic Function in Patients After the Disappearance of Icterus*

(1) Excretion of urobilinogen was abnormal in 77% of 18 cases
(2) Retention of sulfobromophthalein was abnormal in 43% of 46 cases
(3) Cephalin-cholesterol flocculation was abnormal in 38% of 34 cases
(4) Activity of serum alkaline phosphatase was abnormal in 30% of 10 cases

Summary.—On the basis of the data presented in tables 1 and 2 it is fair to conclude that of the tests studied the quantitative test for excretion of urobilinogen in the urine is the least likely to yield normal results during the period of jaundice and is the most likely to reveal abnormality immediately after the jaundice has disappeared.

SUMMARY AND CONCLUSIONS

A. One hundred and twenty cases of acute infectious hepatitis with jaundice were studied during the height of the disease and well into the convalescent period, a variety of the more sensitive tests of hepatic function being used.

B. Of the tests used, the quantitative method for determining the excretion of urobilinogen in the urine was found to be the most valuable. It was the test least likely to give normal results while jaundice was present and the one most likely to give abnormal results after jaundice had subsided.

C. Because of the simplicity of the test, serial studies of quantitative excretion of urobilinogen in the urine should be made at least every other day during the convalescent period of a patient with infectious hepatitis and interpreted in the light of this individual patient. Because of the wide fluctuations of excretion of urobilinogen in the urine during convalescence, a spot check may be misleading and normal values will be falsely interpreted.

PNEUMONIA ASSOCIATED WITH VARICELLA

Review of the Literature and Report of a Fatal Case with Autopsy

WILLIAM D. CLAUDY, M.D.
Associate in Medicine, Doctors Hospital
WASHINGTON, D. C.

IT HAS not been generally appreciated that varicella may occasionally assume the form of a rather severe disease, especially in adults, nor is pneumonia recognized as a common complication of this disease. A review of the medical literature on the subject shows a paucity of articles regarding it, and only 1 fatal case with autopsy observations has been described. It is therefore considered worth while to add another case to the literature, particularly as careful postmortem studies, including attempts at virus transfers, were undertaken.

Waldman [1] described a case of chickenpox in a Negro girl 8 years of age, in whom acute rheumatic endocarditis developed during the course of an ordinary uncomplicated attack, followed by lobar pneumonia of the lower lobe of the right lung, with a fatal termination on the tenth day of the disease. Autopsy was not permitted, but it was Waldman's opinion that the condition represented a concurrent infection rather than a complication.

Bullowa and Wishik,[2] studying 2,534 patients with chickenpox admitted to the Willard Parker Hospital in a four year period, found 8 deaths, 1 that of a patient over the age of 30. In the remaining cases the disease occurred in children less than 6½ years of age. In each of these cases slight to severe lobular pneumonia was described at autopsy. In this same series complications were noted in 5.2 per cent of all cases, pneumonia occurring in 0.8 per cent or representing one seventh of the complications.

Waring, Neubuerger and Geever [3] described 2 cases of varicella and pneumonia, in 1 of which there was a fatal outcome; careful postmortem studies were made. A 40 year old man was admitted to the hospital

1. Waldman, S.: Complication, or Concurrence in a Case of Chickenpox Associated with Rheumatic Endocarditis and Fatal Pneumonia, M. Rec. **155**:9-10 (Jan. 7) 1942.

2. Bullowa, J. G. M., and Wishik, S. M.: Complications of Varicella: Their Concurrence Among 2,534 Patients, Am. J. Dis. Child. **49**:923-926 (April) 1935.

3. Waring, J. J.; Neubuerger, K. T., and Geever, E. F.: Severe Forms of Chickenpox in Adults with Autopsy Observations in a Case with Associated Pneumonia and Encephalitis, Arch. Int. Med. **69**:384-408 (March) 1942.

three days after the onset of his illness on Dec. 27, 1940. He gave a definite history of exposure to chickenpox through his son, who was convalescing from the disease. On admission to the hospital he was cyanotic and dyspneic, coughing frequently and expectorating a thick, tenacious and bloody sputum. He had a heavy but typical varicella eruption. The leukocyte count was 15,250, with 73 per cent neutrophils. Repeated smears and culture of the sputum failed to reveal pneumococci. Roentgenologic examination of the chest showed bronchopneumonia, with a widespread mottling through both lungs, most pronounced at the bases. In spite of intensive supportive treatment and the administration of sulfathiazole, progressive nitrogen retention developed, and he went into coma and died early on the seventh day of the disease. Postmortem examination disclosed (1) severe generalized chickenpox, (2) lobular pneumonia which was severe, confluent, mononuclear and proliferative, (3) acute, toxic, moderate, diffuse encephalitis with purpura of the white matter and (4) acute, toxic, moderate nephrosis.

The second patient was a 33 year old man with a definite history of exposure through his daughter. Severe chickenpox, acute bronchopneumonia, profuse bright bloody sputum, dyspnea, cyanosis, delirium, moderate nitrogen retention, pleurisy and osteomyelitis of the jaw developed, but he eventually recovered. He was first treated with sulfathiazole, and later given sulfanilamide when a pure culture of streptococcus was obtained from the sputum. He also received convalescent streptococcus serum, to which the authors give considerable credit for his eventual recovery.

Rausch, Grable and Musser [4] present a report of a case of severe varicella in a 27 year old white male physician, complicated by pneumonia (said on roentgenologic examination to be a bronchopneumonic infiltration of both pulmonary fields) and by laryngeal spasm; the patient responded well to treatment with sulfathiazole.

An unusually severe outbreak of varicella among the natives of the French Cameroon district in 1936 was described by Millous.[5] There were 1,919 cases, with 370 deaths, mostly involving adults. The disease appeared regardless of the smallpox vaccination which had been extensively employed in that area, with typical varicella lesions appearing in crops. In cases with a fatal outcome death was attributed either to nephritis with uremia or to severe laryngitis with prominent dysphagia and dysphea. Unfortunately, no pathologic studies were reported for this outbreak.

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4. Rausch, L. E.; Grable, T. J., and Musser, J. H.: Atypical Pneumonia Complicating Severe Varicella in Adult, New Orleans M. & S. J. **96**:271-275 (Dec.) 1943.

5. Millous: Une épidemie de varicelle maligne au Cameron, Bull. Acad. de méd., Paris **115**:840-843 (June 16) 1936.

REPORT OF A CASE

The patient involved was a white housewife aged 32. On April 13, 1944, her 8½ year old son became ill with typical chickenpox. The disease ran its usual mild course without complications. On April 25 the patient complained to her husband that she did not feel as well as usual but continued her housework. On April 27 a typical chickenpox eruption commenced to break out, beginning over the head and thorax. Simultaneously, similar eruptions developed in the patient's other two children. All 3 were seen by a pediatrician, who made a diagnosis of chickenpox. The children had been successfully vaccinated against smallpox, and the patient herself thought that she had been vaccinated in childhood, although no scar was present.

On April 28 the patient commenced to complain of cough and abdominal pain, and on the advice of her pediatrician she called in an internist. She was first seen on April 29 at about 10 p. m. Physical examination at that time revealed a well nourished and well developed white woman, aged 32, whose arms, face and body were covered by a heavy maculopapular eruption in various stages and who appeared to be in moderate distress but not severely ill. She had a dry, harsh, nonproductive cough, which had been present for about eighteen hours, and also complained of vague colicky pain throughout the abdomen. There had been no nausea, vomiting or diarrhea and no hemoptysis. The temperature was 102 F. by mouth, the pulse rate 110 per minute and the respirations 20 per minute. The nose was moderately congested, and there were several enanthematous lesions over the palate and the buccal mucous membranes. One small pock was noted on the posterior pharynx. The face was covered with a heavy, typical varicella rash, which had spread over the thorax and axillary regions and which became lighter as it spread distally down the arms. A few lesions were noted on the legs, and one pock was noted on the palm of the left hand and one on the sole of the left foot. The lungs revealed somewhat roughened breath sounds at both apexes but were otherwise completely clear. The abdomen was soft and not tender. The heart was within normal limits on percussion and palpation. The rate was 110 per minute, the rhythm regular and the sounds of good quality, with no murmurs audible.

Calamine lotion had been used for the rash, and the patient was told that she might continue with the use of this. A cough mixture containing a small quantity of codeine was prescribed, and steam inhalations of tincture of benzoin were commenced.

On the morning of April 30 she complained of tightness in the chest, which became progressively severer and was accompanied with increasing dyspnea through the day. At noon she commenced to cough productively and brought up quantities of blood-tinged sputum. The temperature rose to 103.8 F. At this time she was admitted to the isolation ward of the Gallinger Municipal Hospital.

A review of systems was noncontributory. The past medical history revealed that the patient had had pneumonia as a young girl, from which she had recovered without difficulty. She had had one or two bouts of secondary anemia, which had responded to iron therapy, and her appendix had been removed. The family history revealed both parents to be living and well, and there was no history of familial disease. The husband, 36 years old, had had chickenpox and was perfectly well.

When admitted to the hospital, she was acutely ill, dyspneic and cyanotic. The rash was a little heavier than previously but was not confluent. The temperature was 102.6 F. by rectum, the pulse rate was 120 per minute, and the

respirations were short, shallow and rapid (50 per minute). There was considerable cyanosis of the lips and ears. Examination of the lungs revealed dulness on percussion over the left side of the chest, both anteriorly and posteriorly, extending over the entire lower two thirds, numerous harsh crepitant rales and scattered areas of tubular breathing in the left infraclavicular area. On the right side there was no impairment of resonance, but there were numerous inspiratory crepitant rales at the base. The observations in the remainder of the examination were essentially the same as those made in the home.

Immediately on the patient's admission to the hospital, sputum and blood were taken for typing and culture of the pneumococci, after which the patient was given 4 Gm. of sulfadiazine by mouth and then 1 Gm. every four hours. The temperature rose from 101 F. on admission to 104 F. on the following day and thereafter varied from 102.5 to 104 F., reaching 104.8 F. on the sixth day of the

TABLE 1.—*Results of a Blood Count and a Urinalysis in the Patient Studied*

				Blood Count						
				Differential Count, %				Schilling Index, %		
Date	Red Blood Cell Count	Hemoglobin, %	White Blood Cell Count	Neutrophils	Lymphocytes	Monocytes	Eosinophils	Segmented Cells	Band Cells	Young Forms
4/30	4,510,000	88*	9,200	69	29	2	..	58	9	2
5/ 2	4,130,000	80	7,400	75	25	2	1	67	4	1
5/ 4	4,030,000	70	11,300	87	11	..	2	70	16	1

	Urinalysis						
Date	Appearance	Reaction	Specific Gravity	Albumin	Sugar	Acetone and Diacetic Acid	Microscopic
5/1	Dark amber	Acid	1.026	2+	Negative	Negative	A few hyaline and finely granular casts, 3 to 4 white blood cells per high power field; a few red blood cells and a few white blood cells; moderate number of hyaline and finely granular casts; few red blood cells and white blood cells per high power field
5/3	Clear amber	Acid	1.015	2+	Negative	Negative	
5/4	Dark amber	Acid	1.018	2+	Faint trace	Negative	

* Newcomber.

illness. From this point there was a gradual but steady fall until death occurred. The pulse rate varied from 110 to 160 per minute and the respirations from 36 to 60 per minute.

Sputum.—On April 30 occasional pus and epithelial cells were found in the sputum, along with considerable blood. There were many gram-positive cocci, which appeared to be staphylococci and streptococci. There were no eosinophils, and no pneumococci were found on direct Neufeld typing. Culture revealed an occasional colony of type IV pneumococci (which in the opinion of the pathologist was due to a contamination from the mouth), Streptococcus viridans, Staphylococcus aureus and Micrococcus catarrhalis. No tubercle bacilli were cultured. On May 2 no pneumococci were found on direct Neufeld typing, and none were present on culture; there were no tubercle bacilli. Str. viridans, Staph. aureus and M. catarrhalis were again recovered.

Roentgen Examination.—Examination of the chest made on May 1, 1944 with portable x-ray equipment showed a homogeneous density in the lower half of the left lung and a diffuse bronchopneumonic type of infiltration throughout the remain-

ing portion of the pulmonary fields. The leaflets of the diaphragm were partially obscured by the infiltration. The heart and great vessels appeared to be within normal limits.

Course in Hospital.—Immediately on the patient's admission to the hospital, oxygen was administered by nasopharyngeal catheter. After eighteen hours an oxygen tent was used because the catheter proved irritating. The patient became progressively worse. On May 2 physical examination revealed complete involvement of the left side of the chest and considerable spread on the right, with rales and dulness over the lower two thirds both anteriorly and posteriorly. Hemoptysis continued, although less pronounced than on the date of admission.

After the finding of a prolonged bleeding time coagulation time and prothrombin time on May 2, therapy with vitamin K was commenced. The patient was given 1.0 cc. intravenously. This was repeated in one hour, and then 20 drops were administered by mouth every four hours.

On May 3 the dosage of sulfadiazine was reduced to 0.5 Gm. four times daily, because of the high level (20 mg.) present in the blood.

By May 4 the patient was irrational at intervals. Respiration continued to be rapid and labored, and she was cyanotic even with continuous administration of oxygen. At 7 p. m. the dyspnea and cyanosis suddenly became much worse, the

TABLE 2.—*Results of Blood Tests*

Blood Culture	Blood Sulfadiazine Levels, %	Bleeding Time	Coagulation Time	Prothrombin Time	Nonprotein Nitrogen
4/30 : Negative 5/ 2 : Negative	5/1 : 5 mg. 5/3 : 20 mg. 5/5 : 8 mg.	5/2 : 4 min. 30 sec.	4 min.	70 sec. (quick) 55 sec.	5/2 : 40 mg.

blood pressure fell to 70 systolic and 20 diastolic and there were other evidences of peripheral circulatory collapse. She received 250 cc. of blood plasma, 1,000 cc. of 5 per cent dextrose in isotonic solution of sodium chloride and 5 cat units of digifolin intravenously. She was then rapidly digitalized by the intramuscular administration of 1 cat unit every four hours for six doses. She responded well, and within three hours the blood pressure had returned to 110 systolic and 70 diastolic and she was partially oriented.

On May 5, at 6 a. m., the patient again appeared moribund. The respirations were 60 per minute, and the pulse rate was 120 per minute, being weak but regular. The blood pressure was 110 systolic and 60 diastolic, and she was unconscious. She rallied spontaneously from this episode, but her condition continued critical. She varied from a muttering delirium to violent attempts to pull the oxygen tent from her, screaming at intervals and apparently having vivid hallucinations. Reexamination of the chest late that afternoon revealed almost complete involvement of all pulmonary fields anteriorly. She was considered too ill to turn or be removed from the oxygen tent for posterior examination. Cyanosis and tachypnea persisted. At 10 : 56 that evening she suddenly died.

Treatment in addition to that already outlined included parenteral and oral administration of fluids to a level of 4,000 to 5,000 cc. in twenty-four hours. Pentobarbital sodium and codeine were used to allay pain and restlessness. Two hundred and fifty cubic centimeters of citrated whole blood was administered on May 3. On May 4 she received 150 cc. of whole blood from her convalescent 8 year old son, followed by 250 cc. of plasma. On May 5 she was given 500 cc. of

citrated blood from a patient who had recovered from varicella about three months previously.

Autopsy.—Postmortem examination was performed about nine hours after death. The body was that of a well developed and well nourished white woman. All the cutaneous surfaces were covered with a papular conical eruption. The centers of these lesions were slightly umbilicated, with crusting, and many showed hemorrhage. Some of the lesions were flatter and more vesicular, although the papular configuration was almost constant. They were not numerous on the scalp, and the skin between the lesions was not distended or otherwise abnormal. No lesions were noted on the conjunctiva or in the mouth.

On section, there was a normal layer of subcutaneous fat and the muscles were well developed. There was no free fluid in the abdominal cavity, and the abdominal organs appeared superficially normal. There was about 50 cc. of straw-colored fluid in each pleural sac, and a small amount of fibrin was present. The pericardial sac contained a normal amount of clear fluid.

The digestive tract showed a few small hemorrhages in the crests of the intestinal folds but was otherwise normal.

Spleen: The spleen was of average size, weighing 150 Gm. It showed several tiny white nodules 1 to 3 mm. in diameter in the capsule. Some of these were umbilicated and had small hemorrhages in their centers. Superficially, they resembled tubercles except for the umbilication. On section, the lymph follicles were prominent in the pulp and no lesions were noted on the cut surface.

Kidneys: The kidneys were both slightly larger than average, but their capsules stripped easily, leaving a smooth surface. On section, the parenchyma appeared normal save for slight cloudiness. A single small hemorrhage was noted in the cortex of the right kidney, just beneath the capsule, but its configuration was not unusual. Small hemorrhages were noted in the mucosa of the pelves, but they were otherwise normal.

The pancreas, bladder, uterus, adnexa and adrenal glands all appeared normal.

Liver: The liver showed a number of flat white nodules in the capsule on the upper surface of the right lobe near the anterior margin. Several of these were umbilicated and slightly raised above the surface, and hemorrhage was present in their centers. They varied from 2 to 5 cm. in diameter. They extended about 1 mm. into the parenchyma, but no other lesions were seen on section. The parenchyma was soft and pale. The gallbladder and bile ducts were normal.

The abdominal and mediastinal lymph nodes were slightly enlarged, soft and pale but showed no other unusual changes.

Lungs and Pleura: The pleural surfaces of both lungs showed scattered flat nodular lesions 3 to 8 mm. in diameter and were slightly raised above the surrounding surfaces. They were reddish white, and the centers were frequently depressed and showed hemorrhage. On section, there was extensive consolidation of all lobes of both lungs. The consolidation was widely scattered and consisted of numerous small nodules, usually about 5 mm. in diameter and frequently coalescent. Many of these nodules were hemorrhagic. They were more numerous in the lower lobes but were clearly evident in all the lobes. There was much congestion and edema in the lower lobes, but the upper lobes were more uniformly consolidated, with less congestion. The bronchi contained thick mucoid material, sometimes streaked with blood. The mucosa of the bronchi, trachea and larynx was slightly congested, but no distinctive lesions were found.

The heart and pericardium appeared normal.

Head: The calvarium and meninges appeared normal, and the external surface of the brain showed no abnormalities.

Microscopic Examination.—The lungs showed focal areas of pneumonic consolidation, especially about the small bronchi. The exudate was composed of fibrin and leukocytes, with polymorphonuclear leukocytes relatively inconspicuous. Small scattered areas of necrosis were also noted. In several areas there were prominent hyaline membranes lining the alveoli.

The liver showed necrosis of the cells in the central portions of the lobules, and there were deposition of fibrin and leukocytic infiltration. There were small nuclear inclusion bodies in some of the hepatic cells. No suppuration was evident.

The spleen showed focal areas of necrosis in, and just beneath, the capsule. These were somewhat larger than miliary tubercles. In these areas the tissues were disintegrated, and there were many fine granules, apparently derived from nuclear disintegration. The remainder of the pulp showed engorgement with red cells and leukocytes. The sinuses were large and distended.

Section of the skin revealed two crusted lesions showing ulceration of the surface epithelium. There was moderate leukocytic infiltration at the base of the ulcers but no distinct granulation tissue. Questionable inclusion bodies were noted in the nuclei of the epithelial cells.

The brain, pituitary, pancreas, adrenals, thyroid, kidneys and uterus showed no significant pathologic changes.

Tissues were obtained in glycerin and forwarded to the National Institute of Health for virus studies. Dr. Armstrong's report on their examination was as follows: "The material from your suspected fatal case of chickenpox was inoculated into monkeys, rabbits, rice rats and mice. All animals remained normal except 1 rabbit, which died in nine days of undetermined cause. Attempts at further transfers were unsuccessful."

COMMENT

The thought immediately arises as to whether this case might not have been an instance of atypical smallpox rather than of true varicella. The severe complications and fatal outcome, plus the absence of a scar from smallpox vaccination, suggest this possibility.

Militating against this diagnosis are: first, the presence of typical chickenpox in 1 child in the family plus the simultaneous occurrence of the disease in the other 2 children (who had been successfully vaccinated against smallpox) and the mother within the expected incubation period; second, the history of vaccination in the mother, and, third, the typical varicella character and distribution of the cutaneous lesions (vesicular eruption with umbilication appearing in crops and concentrated most heavily on the head and trunk). The weight of this evidence seems definitely in favor of a diagnosis of chickenpox.

The similarity of the 2 cases reported by Waring, Neubuerger and Geever to this one is striking, with the rapid early pulmonary involvement and the hemoptysis being outstanding in all 3.

It is unfortunate that the virus transfers attempted at the National Institute of Health were not successful. The reasons for this may have been: (1) the length of time between the outbreak of the disease and its fatal termination on the eighth day and (2) the length of time elapsing

between death and the performance of the postmortem examination (twelve hours).

A striking feature of the postmortem examination was the presence of what were apparently varicella pocks on the pleura, within the pulmonary tissue and on the peripheral portions of the liver and spleen. Microscopic examination confirmed the apparently pocklike nature of these lesions.

SUMMARY

The literature relating to fatal cases of varicella (chickenpox) is reviewed, and an additional fatal case, with postmortem studies and attempts at virus transfer, involving a previously healthy adult is presented.

It is again emphasized that a disease, usually considered to be a relatively harmless and innocuous one, may on occasion become severe and fulminating.

The study of this case was aided by the National Institute of Health and Dr. Armstrong, responsible for the attempted virus transfer; Dr. Arnold McNitt and Dr. Roy Adams, of Washington, D. C., who saw the patient in consultation, and Dr. Thomas Peery and Dr. Roger Choisser, of the Department of Pathology of the George Washington University Medical School, who made the careful postmortem examination.

CONCENTRATION TEST OF RENAL FUNCTION USING POSTERIOR PITUITARY INJECTION

An Evaluation

NORMAN G. SCHNEEBERG, M.D.
PHILADELPHIA

THE ability of the normal kidney to produce a concentrated urine under conditions of diminished intake of fluid is usually the first function to fail under the influence of renal disease. Procedures designed to test this function of the kidney are the most useful and the least complicated to perform. The technics described by Fishberg [1] and by Addis and Shevky [2] are time-tested standards for routine use. They require the production of oliguria by depriving a tested subject of fluids over an interval of from sixteen to twenty-four hours and the measurement of the specific gravity of samples of urine voided at the end of this period of restriction. The maximum specific gravity necessary for evaluation of renal concentrating capacity may not be attained under the following conditions: (*a*) if the patient fails to cooperate, often because of excessive thirst, and drinks fluid during the period of deprivation; (*b*) if the period of abstinence from fluids is not sufficiently long to test renal concentrating capacity adequately in patients who have been drinking excessive amounts of fluid prior to the test, or (*c*) if edema fluid is being cleared.

Utilization of the antidiuretic action of posterior pituitary extract to eliminate the period of imposed interdiction of fluid and thus to circumvent sources of error and to simplify the performance of renal concentration tests was first thoroughly investigated by Sodeman and Engelhardt,[3] though references to similar procedures have appeared

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At present Dr. Schneeberg is a fellow of the Department of Endocrine and Metabolic Research, Michael Reese Hospital.

Part of this work was done while Dr. Schneeberg was at the Mount Sinai Hospital in Philadelphia, and part was done while he was in army service.

1. Fishberg, A. M.: Hypertension and Nephritis, ed. 4, Philadelphia, Lea & Febiger, 1939, p. 74.

2. Addis, T., and Shevky, M. C.: A Test of the Capacity of the Kidney to Produce Urine of High Specific Gravity, Arch. Int. Med. **30**:559-562 (Nov.) 1922.

3. Sodeman, W. A., and Engelhardt, H. T.: (*a*) Renal Concentration Test Employing Use of Pituitary Extracts: Response of Normal Subjects, Proc. Soc. Exper. Biol. & Med. **46**:688-691 (April) 1941; (*b*) A Renal Concentration Test Employing Posterior Pituitary Extract, Am. J. M. Sc. **203**:812-818 (June) 1942.

in the literature since 1921.[4] Their test now appears in a standard text of laboratory procedures,[5] and its use has been advocated in two recent reviews.[6] Wall,[7] Taylor, Peirce and Page[8] and Schneeberg, Likoff and Rubin[9] have published their experiences with this test, with varying conclusions as to its acceptability for general use. Concern for possible untoward effects of posterior pituitary has been expressed. It is my intent to reevaluate this procedure and to show the effect of administration of posterior pituitary (posterior pituitary injection U.S.P. was used) on the electrocardiogram, the blood pressure and the pulse rate of patients subjected to the test.

METHODS

A. *Renal Concentration Tests.*—Renal concentration tests were as follows: (1) the Fishberg concentration test, which was performed as outlined by its author[1]; (2) the concentration test with posterior pituitary injection, in which, without restriction of fluid or food, the patient emptied his bladder, 10 units of posterior pituitary was injected subcutaneously and three specimens of urine were obtained hourly thereafter; (3) the Volhard dilution test, in which the subject emptied his bladder and drank 1,500 cc. of water within thirty minutes and then four hourly specimens of urine were collected; (4) a test in which procedure 3 was repeated with the addition of 10 units of posterior pituitary injected subcutaneously after the ingestion of the fluid; (5) the Addis concentration test; in this test the subject abstained from fluid for twenty-four hours (from after breakfast of one day until arising the next morning) and then the urine of the last twelve hours of this period was collected and the specific gravity measured.

The specific gravity of the urine was measured with a clinical urinometer calibrated with distilled water at a standard temperature. Appropriate corrections for variations in temperature[10] and protein content[11] were made.

Procedures 1 and 2 were carried out on 136 subjects comprising 101 normal persons and 35 with varying evidences of renal disease. For 25 of the normal subjects procedures 1, 2, 3 and 4 were carried out, and 15 additional persons

4. Brunn, F.: Pituitary Extract as Kidney Test, Med. Klin. **17**:871 (July 17) 1921.

5. Gradwohl, R. B. H.: Clinical Laboratory Methods and Diagnosis, ed. 3, St. Louis, C. V. Mosby Company, 1943, vol. 1, p. 133.

6. Talbott, J. H.: Medical Progress: Renal Function Tests, New England J. Med. **226**:197-201 (Jan. 29) 1942. Ross, J. F.: Common Laboratory Aids to Diagnosis and Treatment, M. Clin. North America **26**:1391-1410 (Sept.) 1942.

7. Wall, H. C.: A Renal Concentration Test Using Solution of Posterior Pituitary Extract, Arch. Int. Med. **71**:454-459 (April) 1943.

8. Taylor, R. D.; Peirce, J. D., and Page, I. H.: Use of Posterior Pituitary Extract in Tests of Urinary Concentration, Am. J. M. Sc. **209**:235-240 (Feb.) 1945.

9. Schneeberg, N. G.; Likoff, W. B., and Rubin, I. E.: The Pituitrin Concentration Test of Renal Function, J. Lab. & Clin. Med. **28**:757-761 (March) 1943.

10. Gradwohl, R. B. H.: Clinical Laboratory Methods and Diagnosis, St. Louis, C. V. Mosby Company, 1935, p. 50.

11. Lashmet, F. H., and Newburgh, L. H.: Improved Concentration Test of Renal Function: Simple Method for Measuring Proteinuria, J. A. M. A. **100**: 1328 (April 29) 1933.

were subjected to procedures 1, 2 and 5. For the purposes of this study a specific gravity of 1.020 was arbitrarily chosen as a basis for the division of the patients into two groups. Those with a concentration of 1.020 or better were considered "normal" and those with a concentration of 1.019 or less were considered "abnormal." In the Addis test the patient was considered normal if a specific gravity of 1.026 or higher was attained.

B. *Cardiovascular Investigation of the Effects of Posterior Pituitary Extract.*—These observations were made in a small, well ventilated, warm room free of external sources of stimulation. All procedures were carried out by me. The subject lay supine on a bed for forty-five to sixty minutes, after which the pulse rate and blood pressure were taken every five minutes until a stabilized level was maintained. Subjects with labile pressures or variable pulse rates were not used. Electrodes were then applied, and an electrocardiogram in the limb leads and CF IV was taken. The blood pressure and pulse rate were again checked to

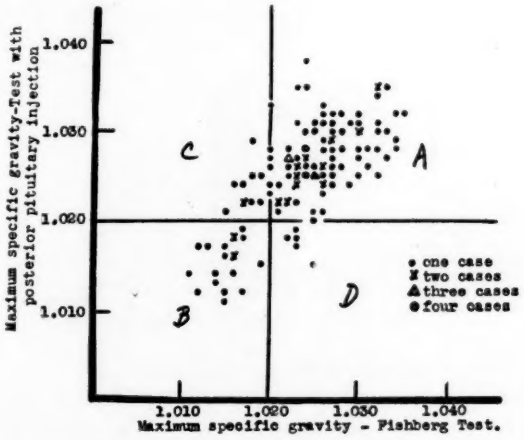

Chart 1.—A comparison of the maximum concentrations of urine obtained by the Fishberg test and by the test with posterior pituitary injection.

insure that the basal level was maintained, and 10 units of posterior pituitary was injected subcutaneously. The blood pressure and pulse rate were taken thereafter every five minutes for a half hour and at forty-five, sixty and ninety minutes. Electrocardiograms in the four leads were taken ten, twenty, thirty, forty-five, sixty and ninety minutes after the injection. The sphygmomanometer cuff and the electrodes were left in place throughout the experiment.

In 5 patients the blood pressure and pulse rate were similarly measured before and after the subcutaneous injection of 0.5 cc. of sterile isotonic solution of sodium chloride.

RESULTS

A. *Renal Concentration Tests.*—In chart 1 the maximum concentrations of urine obtained by the use of posterior pituitary injection and by the Fishberg test are given for 136 cases. One hundred and two of these patients, comprising group A of the graph, had a concen-

tration of 1.020 or better by both tests, exhibiting, according to the criterion established, normal concentrating ability. Nineteen patients, comprising group B on the graph, had a concentration of 1.019 or less by both tests, exhibiting an inability to concentrate urine normally. In group C, comprising 10 cases, the tests failed to achieve comparable results. Normal concentrations of urinc were obtained by the use of posterior pituitary injection when, in the same patient, abnormally dilute urine was obtained in the Fishberg test. In group D, comprising 5 cases, the tests again failed to yield comparable results. In these cases the Fishberg test produced a normally concentrated urine and the test with posterior pituitary an abnormally dilute urine. Thus the posterior pituitary test failed to estimate renal concentrating capacity properly in 3.7 per cent of the 136 cases, and the Fishberg test similarly failed in 7.4 per cent. These stated percentages of failure, how-

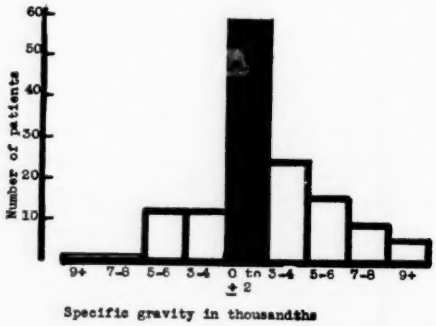

Chart 2.—Distribution graph of the differences between the test with posterior pituitary injection and the Fishberg test in 136 patients. The former test gave the higher value to the right of the solid block, and the latter gave the higher value to the left.

ever, are not significant, because a change of the arbitrarily established criterion of normal from 1.020 to 1.022 or 0.023 will greatly alter the results. The individually plotted specific gravities in chart 1 are well grouped about a straight line curve, and the distribution graph shows a normal scatter about the mean. The only conclusion that is justified, therefore, is that in the 136 cases examined the two tests yielded similar results.

In chart 2 the distribution of the differences between the two tests is graphed. In 17 patients identical maximum specific gravities were obtained by the test with posterior pituitary injection and the Fishberg test. The former test yielded the higher specific gravity in 79 cases, and the latter yielded the higher result in 40 cases. The difference in specific gravity in the two tests was 0.004 or less for 69 per cent of the 136 patients and 0.006 or less for 89 per cent.

Chart 3 graphically illustrates a comparison of three tests for concentration of urine performed on the same patient (procedures 1, 2 and 5). In 11 patients the results in all three tests agreed, 6 showing normal concentration of urine and 5 abnormal concentration. In 4 cases in which the Addis test and the posterior pituitary test showed normal results, the Fishberg test gave abnormal values. Thus the posterior pituitary and the Addis test agreed in their estimate of renal function in all 15 cases.

In the 25 subjects in whom procedures 3 and 4 were performed, the average specific gravity was 1.006 as obtained by procedure 3 and 1.024 as obtained by procedure 4. This indicated the potency of the preparation of posterior pituitary injection used.

B. *Cardiovascular Investigation.*—No significant changes were noted in the electrocardiograms taken after the injection of the posterior

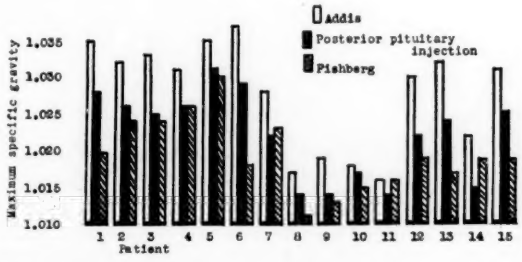

Chart 3.—A comparison of three concentration tests of renal function performed on each of 15 patients.

pituitary extract. The seven tracings obtained in each patient either were identical or showed insignificant variations.

Chart 4 graphically portrays the changes in blood pressure noted after the use of posterior pituitary injection compared with the blood pressure in controls who received injections of isotonic solution of sodium chloride. The mean curves for the two groups are similar except for the systolic and diastolic rise, which occurred five minutes after the injection of posterior pituitary extract and subsided to the basal level within fifteen minutes for the systolic pressure and twenty minutes for the diastolic pressure. Since this change was not observed in the control patients, it appears to be a specific effect of the pituitary extract. The gradual fall in average pressures below the basal level probably represents the effect of the long-continued supine position that the experiment entailed, since it was noted in both groups. In individual cases a much greater rise or fall from the basal level was encountered in the subjects receiving posterior pituitary injection than in the controls receiving isotonic solution of sodium chloride. This

is evidenced by the widely scattered systolic pressure readings in chart 4.

Posterior pituitary injection caused a slight rise in the mean pulse rate (4½ per minute, with a range of plus 18 to minus 8) in the five and ten minute periods after the injection, which did not occur in the controls. This acceleration of the pulse rate was, therefore, probably due to the action of the pituitary extract rather than a nonspecific reaction to a hypodermic injection.

COMMENT

The data presented indicate that the use of posterior pituitary injection in renal concentration tests in 136 patients yielded results that

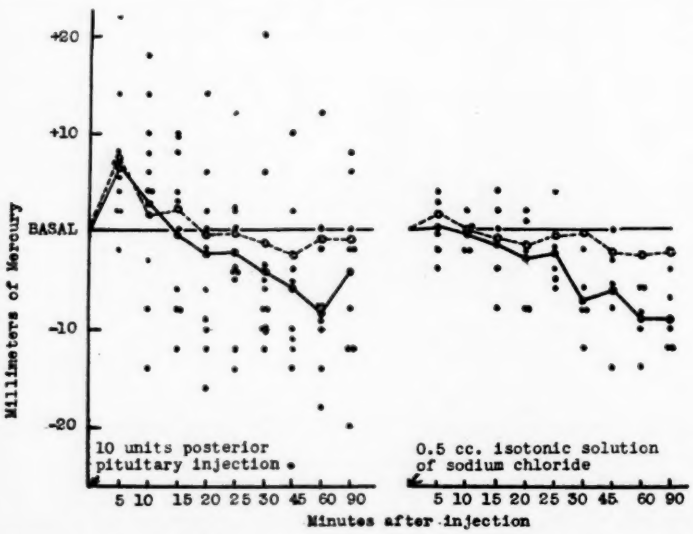

Chart 4.—Mean changes in blood pressure after the subcutaneous injection of posterior pituitary extract in 10 patients and normal isotonic solution of sodium chloride in 5 controls. Unconnected points are individual systolic pressure readings. The broken line indicates the mean diastolic pressure and the unbroken line the mean systolic pressure.

were similar to those obtained in the standard Fishberg test. The test with posterior pituitary injection may, therefore, be used routinely whenever a concentration test of renal function is indicated.

While Sodeman and Engelhardt [3] and Wall [7] found the posterior pituitary test reliable, Taylor, Peirce and Page [8] concluded that it was not entirely acceptable in clinical practice. They compared it with the procedure, outlined by Addis and Shevky,[2] in which fluids are interdicted for twenty-four hours. Much greater average concentra-

tions of urine were promoted by the Addis test than by the posterior pituitary test or by the use of pitressin tannate in oil, short periods of dehydration and combinations of these. Said the authors: "None of these procedures attained the mean concentration of 1.030 recorded after 24 hours dehydration in normal subjects." The range of variation in them was from 1.016 to 1.033, compared with 1.026 to 1.032 in the Addis test. Similar variability was observed in abnormal subjects receiving pituitary extracts. They also discussed untoward effects resulting from the injection of posterior pituitary extract.

In the present study the Addis test was compared with the Fishberg test and the posterior pituitary test in the same patients, and it was found that a twenty-four hour fast from fluids gave no more useful information than did the posterior pituitary test in the subjects investigated. In each instance both technics yielded results which agreed in the estimation of tubular concentrating ability according to the standards established. The results of this comparison in chart 3 show that the Addis test produced the highest specific gravity in 14 of the 15 patients and that in the remaining patient (case 11) both the Addis and the Fishberg test produced a specific gravity of 1.016 and the posterior pituitary test a value of 1.014. If, however, one accepts 1.026 as the normal value for the Addis test,[2] a similar failure to achieve normal concentrations of urine was noted in the same patients exhibiting impaired concentrating ability by the other tests. The Fishberg test and the posterior pituitary test do not give ceiling values, but they do give results that are consistent and clinically applicable. The Addis test requires a twenty-four hour period of abstinence from fluid and can be properly performed only in a hospital ward adequately staffed to control the conditions of the test.

The test with posterior pituitary injection is ideally designed for office practice because of its simplicity, the speed with which results are obtained and the elimination of the hardship imposed on the patient by abstinence from fluid and by the necessity of carrying urine to the office. Unlike the tests requiring the interdiction of fluids, it will not fail to produce a concentrated urine even if the patient is edematous.[7] Its effect is dissipated within six hours, and edematous reservoirs can be cleared as before. In febrile or surgical patients in whom deprivation of fluid is not desired, the test with posterior pituitary injection may be used when the Addis or Fishberg test would be impractical.

Significant cardiovascular changes were not produced by the injection of the recommended dose of posterior pituitary used in the test for renal function aside from a transient rise in blood pressure and

increase in pulse rate in the period immediately following the injection. Similar results have been reported by others.[12]

Because of the well known coronary-vasoconstrictive effect of posterior pituitary, coronary arterial disease and angina pectoris are considered contraindications to its use. Graybiel and Glendy [12c] gave 20 international units of pitressin intravenously to 2 patients with "easily provoked anginal pain." Though this dose was sufficient to provoke abdominal cramps, anginal pain did not occur. Wall's patient with angina pectoris [7] experienced slight substernal distress and tingling down the left arm following the injection of posterior pituitary extract, which promptly disappeared after administration of glyceryl trinitrate. My colleagues and I [9] observed no untoward effects when using the test in patients with coronary arterial disease, but because of the theoretic objections mentioned previously, the tests using deprivation of water are preferred for such subjects. The subcutaneous injection of posterior pituitary extract causes a mild burning sensation at the site of injection, lasting two to three minutes. Most persons experience no subsequent discomfort, though the occasional patient, on being questioned, will describe slight shortness of breath, substernal warmth, a "cool feeling across the chest," a slight "cool sensation all over" or fleeting nausea. Slight pallor of the skin can be observed shortly after the injection in about one quarter of the cases.

The paucity of reports of hypersensitivity to posterior pituitary is striking when one realizes how commonly this extract is used. In more than 350 persons subjected to the posterior pituitary test by various workers, there has been no instance of hypersensitivity or an anaphylactic reaction reported. McMann [13] could find only twelve references to reactions indicating sensitivity up to 1939 and added two of his own. Werner [14] stated that he has had experience with approximately two hundred thousand injections of posterior pituitary extract without harmful results. Grand mal seizures may be precipitated by effective anti-

12. (*a*) Moffat, W. M.: The Effect of Pituitrin Injections on Blood Pressure in Man, Am. J. M. Sc. **186**:854-860 (Dec.) 1933. (*b*) Grollman, A., and Geiling, E. M. K.: Cardiovascular and Metabolic Reactions of Man to Intramuscular Injection of Posterior Pituitary Liquid (Pituitrin), Pitressin and Pitocin, J. Pharmacol. & Exper. Therap. **46**:447-460 (Dec.) 1932. (*c*) Graybiel, A., and Glendy, R. E.: Circulatory Effects Following the Intravenous Administration of Pitressin in Normal Persons and in Patients with Hypertension and Angina Pectoris. Am. Heart J. **21**:481-489 (April) 1941.

13. McMann, W.: Hypersensitivity to Solution of Posterior Pituitary, J. A. M. A. **113**:1488 (Oct. 14) 1939.

14. Werner, A. A.: Endocrinology: Clinical Application and Treatment, ed. 2, Philadelphia, Lea & Febiger, 1942, p. 75.

diuresis with posterior pituitary injection if fluids are forced.[15] One death by such a provocative procedure has been reported.[16] The use of posterior pituitary injection in epileptic patients had best be avoided, though it seems unlikely that the injection of a single dose of 10 units without the administration of extra fluid could precipitate a seizure.

The contraindications to the use of posterior pituitary injection in tests of renal function are as follows:

A. Absolute contraindications.

1. Hypersensitivity to posterior pituitary extract.

2. Pregnancy.

3. Severe coronary arterial disease (myocardial infarction, acute coronary insufficiency or angina pectoris decubitus).

B. Probable contraindications.

1. Angina pectoris.

2. Epilepsy.

In clinical practice the test may be performed as follows:

1. It may be carried out at any time without preparation.

2. The patient voids, emptying his bladder completely. If the specific gravity of this specimen is 1.022 or higher, the test need not be done. If the specific gravity is 1.021 or less, the test is carried out.

3. A 10 unit dose of posterior pituitary injection U.S.P. is introduced subcutaneously.

4. Urine is collected in one and two hours. When the volume of the two specimens is too small to permit measurement of specific gravity with the clinical urinometer, a specimen is collected after three hours.

5. Normal subjects will have a specific gravity of 1.022 or better in one specimen. The criterion of 1.020 used in this study was arbitrarily selected for the purposes of comparing the posterior pituitary test with the Fishberg test.

SUMMARY

1. A comparison of the concentration test of renal tubular function in which posterior pituitary injection is used with the standard Fishberg test in 136 patients showed that this new procedure yields sufficiently similar results to be used routinely as a substitute test.

15. McQuarrie L., and Peeler, D. B.: The Effects of Sustained Pituitary Antidiuresis and Forced Water Drinking in Epileptic Children: A Diagnostic and Etiologic Study, J. Clin. Investigation **10**:915-940 (Oct.) 1931.

16. Muller-Suur, H.: Death Due to Tonephin (Posterior Pituitary Preparation) Injection for Diagnostic Provocation of Epileptic Attack by Water Retention, Psychiat.-neurol. Wchnschr. **44**:137-139 (May 2) 1942.

2. The Addis test, requiring a twenty-four hour fast from fluids, gave no more useful information in the same patient than did the test with posterior pituitary injection, despite its ability to produce ceiling values in most instances.

3. Posterior pituitary injection, in the dose used in this test, produced no significant electrocardiographic changes and only a transient rise in blood pressure and acceleration of pulse rate.

4. Hypersensitivity to posterior pituitary is extremely rare and has not been encountered in the performance of this test.

5. Contraindications to the use of posterior pituitary are outlined.

6. The test is simple to perform and avoids sources of error inherent in tests requiring periods of abstinence from fluid.

1930 Chestnut Street.

STUDIES ON THE CAUSATION OF AN UNUSUAL PULMONARY DISEASE AT CAMP GRUBER, OKLA.

COMMISSION ON ACUTE RESPIRATORY DISEASES
in Collaboration with
FIRST LIEUTENANT WALTER A. MICKLE Jr.
SANITARY CORPS, ARMY OF THE UNITED STATES

Specimens of sputum from 17 patients with pneumonia at Camp Gruber, Okla., have been examined for the presence of an infectious agent which might have caused the illnesses. Most of the sputums were obtained three to four weeks after the onset of the disease, but many of the patients were still febrile at the time of collection. In addition, sputums were collected from 8 patients not involved in this outbreak of pneumonia for the purpose of comparison.

Several samples of dust from a storm cellar, incriminated epidemiologically as a probable source of the infection, and of dirt from a nearby machine gun emplacement were also collected for study.

Cultures, inoculation of animals and serologic tests were carried out. Particular emphasis was placed on mycologic examinations, because of the clinical characteristics of the disease.

EXPERIMENTAL DATA

Cultures for Bacteria.—Cultures for bacteria in the sputums were made on blood agar plates. These were examined after twenty-four and forty-eight hours of incubation. Representative colonies of bacteria were isolated and identified.

No one species of bacteria was predominant in any of the cultures. Small numbers of hemolytic Staphylococcus aureus were recovered from 10 of the 17

From the Respiratory Diseases Commission Laboratory, Regional Hospital, Section 2, Fort Bragg, N. C.

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Members and associates of the Commission on Acute Respiratory Diseases are: Major John H. Dingle, Director; Major Theodore J. Abernethy; Major George F. Badger; Major Norman L. Cressy; Major Alexander D. Langmuir; Capt. Hugh Tatlock, and Capt. Elias Strauss, Medical Corps, Army of the United States; and Dr. J. W. Beard, Dr. A. E. Feller, Dr. Irving Gordon and Dr. Charles H. Rammelkamp.

patients with pneumonia and from 1 control patient. Group A beta hemolytic streptococci were recovered in small numbers from 2 patients. The samples of dust and dirt were not cultured for bacteria.

Cultures for Fungi.—Cultures for fungi were made on Sabouraud's dextrose agar and dextrose-tartaric acid agar. These cultures were examined at intervals for four weeks before they were discarded. Fungi were isolated as soon as they appeared and were identified by standard mycologic methods.

Aspergillus, Penicillium, Mucor, Rhizopus, Alternaria, Fusarium, Saccharomyces and aerobic Actinomyces were isolated from the sputums. These were not identified further. Aspergilli were isolated from 5 patients with pneumonia and Penicillium from 3 patients. Mucor and Rhizopus were isolated from 2 patients each, and Saccharomyces and aerobic Actinomyces occurred only once. Candida pseudotropicalis was isolated from 1 patient. C. albicans was isolated from 10 of the 17 patients, but in only one instance were there more than four colonies on the plate.

Aspergillus was isolated twice and Penicillium and Mucor once from the sputums of the 8 controls.

Samples of dust from the cellar and of dirt from the gun emplacement yielded a variety of molds: Mucor, Aspergilli, Penicillium, aerobic Actinomyces, Alternaria and Rhizopus. No C. albicans was found.

Inoculation of Animals.—Specimens of sputums were inoculated intranasally and intraperitoneally into mice, cotton rats, hamsters, guinea pigs and monkeys. Records of the daily temperature were kept on the hamsters, guinea pigs and monkeys. Roentgenograms of the chest were taken on the monkeys at two to three day intervals before and for six weeks following inoculation.

No evidence of significant illness occurred in any of the animals. One animal of each species in the groups inoculated intranasally and intraperitoneally was killed eleven days after inoculation. None of these animals showed gross or microscopic evidence of infection, and cultures of the internal organs for bacteria and fungi were sterile.

Two strains of C. albicans isolated from sputums of patients with pneumonia were tested for virulence in guinea pigs and rabbits. One cubic centimeter of a 10 per cent suspension was necessary to kill the animals, indicating a relative lack of virulence.

Serologic Studies.—Tests with C. albicans on serums from each of 15 patients in the acute and convalescent stages of pneumonia and from 8 control patients showed no agglutination or complement fixation above a dilution of 0.125 in any case. There were no rises in titer in the serums from convalescent patients.

Agglutinins for the rickettsia of Q fever and cold hemagglutinins for group O human erythrocytes were not found in the serums from convalescent patients.

CONCLUSION

Studies on specimens from patients with pneumonia occurring at Camp Gruber, Okla., have failed to identify a causative agent. Attempts to reproduce the disease in animals were unsuccessful. Although C. albicans was isolated in 10 of 17 patients ill with pneumonia, the role of this organism is questionable because of the lack of supportive evidence.

NOTE.—This material should have been published as supplement to the article by Colonel James C. Cain, Major Edward J. Devins and Lieutenant Colonel John E. Downing, "An Unusual Pulmonary Disease," in June 1947 (Arch. Int. Med. **79**:626, 1947).

RECENT MYOCARDIAL INFARCTION

An Analysis of Five Hundred and Seventy-Two Cases

S. S. MINTZ, M.D.
AND
L. N. KATZ, M.D.
CHICAGO

CONSIDERABLE modification has occurred in the point of view concerning recent myocardial infarction since its first adequate clinical description by Herrick.[1] There is therefore need for further studies of this condition. The present report deals with the cases of recent myocardial infarction in which electrocardiographic studies were made at the Michael Reese Hospital in the period from Jan. 1, 1940 to Dec. 31, 1945. Only the cases were included in which, on the basis of the history, the electrocardiograms and, when available, the observations at autopsy, the condition could unequivocally be diagnosed as a recent myocardial infarct. A total of 572 cases was selected. The patients for the most part were Jews; a few were Negroes.

Of the total of 572 patients, 504 were admitted to the hospital for a six to eight week (rarely a ten week) stay as ward and private patients; on these, complete histories, serial electrocardiograms and the usual laboratory data were available. For 48 of the patients, who were kept at home by their private physicians during the acute stage of the disease, the data available to us consist of electrocardiograms made during convalescence. In addition, their age and sex and the date of the attack are known. The remaining 20 patients, from the outpatient clinic, were also kept at home during the acute stage; information on them was obtained from their physicians, the social service worker, their clinic records and the electrocardiograms taken during the initial and convalescent stages of illness.

From the Cardiovascular Department, Michael Reese Hospital.

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The attending physicians of the patients included in this study permitted us to use the records of their cases and in many instances supplied us with additional information. The members of the department, in particular Dr. R. Langendorf, contributed suggestions and criticisms in the preparation of this report.

1. Herrick, J. B.: Clinical Features of Sudden Obstruction of the Coronary Arteries, J. A. M. A. **59**:2015 (Dec. 7) 1912.

In 529 patients the attack of myocardial infarction under study was their first one as far as could be determined; in the other 43 it was the second attack. Patients having more than two attacks were excluded from this series.

The data so analyzed were correlated with reports in the literature, and certain deductions were made to assist in the formulation of clinical guides, especially as to immediate prognosis. These are to be considered as tentative and subject to revision as larger series are analyzed.

SEX

There were 392 men (68.5 per cent) and 180 women (31.5 per cent), a ratio of 2.2:1. Only Hedley,[2] Bean,[3] Rosenbaum and Levine[4] and Rathe[5] reported similar ratios. Most of the other observers[6] had a higher ratio of men, varying from 13:1 (Parkinson and Bedford[7]) to

2. Hedley, O. F.: Five Years' Experience (1933-1937) with Mortality from Acute Coronary Occlusion in Philadelphia, Ann. Int. Med. **13**:598, 1939.

3. Bean, W. B.: Infarction of the Heart: Morphological and Clinical Appraisal of Three Hundred Cases; Predisposing and Precipitating Conditions, Am. Heart J. **14**:684, 1937.

4. Rosenbaum, F. F., and Levine, S. S.: Prognostic Value of Various Clinical and Electrocardiographic Features of Myocardial Infarction: I. Immediate Prognosis, Arch. Int. Med. **68**:913 (Nov.) 1944.

5. Rathe, H. W.: Myocardial Infarction: Clinical Features and Prognosis, J. A. M. A. **120**:99 (Sept. 12) 1942.

6. (*a*) White, P. D.: The Prognosis of Angina Pectoris and of Coronary Thrombosis, J. A. M. A. **87**:1525 (Nov. 6) 1926. (*b*) White, P. D., and Bland, E. F.: Further Report on the Prognosis of Angina Pectoris and of Coronary Thrombosis: A Study of Five Hundred Cases of the Former Condition and of Two Hundred Cases of the Latter, Am. Heart J. **7**:1, 1931. (*c*) Levine, S. A., and Brown, C. L.: Coronary Thrombosis: Its Various Clinical Features, Medicine **8**:245, 1929. (*d*) Willius, F. A.: Life Expectancy in Coronary Thrombosis, J. A. M. A. **106**:1890 (May 30) 1936. (*e*) Conner, L. A., and Holt, E.: The Subsequent Course and Prognosis in Coronary Thrombosis (An Analysis of Two Hundred and Eighty-Seven Cases), Am. Heart J. **5**:705, 1930. (*f*) Master, A. M.; Dack, S., and Jaffe, H. L.: Age, Sex and Hypertension in Myocardial Infarction Due to Coronary Occlusion, Arch. Int. Med. **64**:767 (Oct.) 1939. (*g*) Appelbaum, E., and Nicolson, G. H. B.: Occlusive Disease of the Coronary Arteries: An Analysis of the Pathological Anatomy in One Hundred and Sixty-Eight Cases with Electrocardiographic Correlation in Thirty-Six of These, Am. Heart J. **10**:662, 1935. (*h*) Goldsmith, G. A., and Willius, F. A.: Bodily Build and Heredity in Coronary Thrombosis, Ann. Int. Med. **10**:1181, 1937. (*i*) Wilhelmy, E. W., and Helwig, F. C.: Clinical and Pathologic Studies of Coronary Disease, J. Missouri M. A. **32**:476, 1935. (*j*) Fisher, R., and Zuckerman, M.: Coronary Thrombosis, J. A. M. A. **131**:385 (June 1) 1946. (*k*) Smith, C.; Sauls, C., and Ballew, J.: Coronary Occlusion: A Clinical Study of One Hundred Patients, Ann. Int. Med. **17**:681, 1942.

7. Parkinson, J., and Bedford, D. E.: Cardiac Infarction and Coronary Thrombosis, Lancet **1**:4, 1928.

3:1 (Mullins[8]). We have therefore confirmed the lesser incidence of myocardial infarction in women but not to the extent previously reported. Apparently the number of women having attacks of myocardial infarction is greater today than it was ten years ago. The cause of this increasing incidence of myocardial infarction in women is unanswered.

AGE

The youngest person in this series was 32 years of age and the oldest 84, and both were men. The average age of the entire group was 60.4 years, that of the women being 62.4 years while that of the men was 58.4 years. In table 1 is shown the distribution of the two sexes by decades. It will be seen that almost 75 per cent of the women had myocardial infarction between the ages of 50 and 70 years, with the greatest number in the seventh decade. About 62.5 per cent of the men had the attack between 50 and 70 years, with the largest number in the

TABLE 1.—*Age Distribution of Recent Myocardial Infarction in Men and Women by Decades*

Decade, Yr.	Men		Women		Total	
	No.	%	No.	%	No.	%
30 to 39	20	5.1	2	1.1	22	3.8
40 to 49	76	19.3	15	8.3	91	15.9
50 to 59	131	32.2	56	31.1	187	32.7
60 to 69	115	29.3	77	42.8	192	33.6
70 to 79	45	11.5	28	15.6	73	12.8
80 to 89	5	1.3	2	1.1	7	1.2
Total	392		180		572	

sixth decade. Almost identical results were obtained by other observers.[9] Master and associates,[6f] however, found infarction at a younger age, most of their patients falling in the period between 45 and 65 years.

MORTALITY DURING THE PATIENTS' STAY IN THE HOSPITAL

Of the 572 patients, 125 died during their stay in the hospital, for the most part within the first two weeks (table 2). This represents a mortality of 21.8 per cent. The mortality among the men was 18.6 per cent and among the women 28.9 per cent. Myocardial infarction thus has a greater rate of immediate fatalities in women than in men. The average age at death was 61.5 years; that of the women was 63.4 years, while that of the men was 59.6 years. The poor prognosis in women

8. Mullins, W. L.: Age Incidence and Mortality in Coronary Occlusion: A Review of Four Hundred Cases, Pennsylvania M. J. **39**:322, 1936.

9. (*a*) Howard, T.: Coronary Occlusion Based on Study of One Hundred and Sixty-Five Cases, M. Times & Long Island M. J. **62**:337, 1934. (*b*) Vander Veer, J. B., and Brown, L. E.: The Diagnosis and Prognosis of Coronary Occlusion: The Electrocardiogram as an Aid, Pennsylvania M. J. **39**:303, 1936.

has also been found by Willius [6d] and Coombs.[10] However, White and Bland [6b] considered sex of no significance in mortality. The greater mortality rate in the women in this series may be due to the fact that they have a greater incidence of diabetes mellitus than do men. Women with myocardial infarction also have a greater frequency of thromboembolic phenomena and arrhythmia than do men and are older at the time of their attack. This will be discussed later. It must be emphasized that this analysis does not give the entire picture of immediate mortality, because many patients die before the physician sees them.

The immediate mortality rate in our series lies between the low mortality rates found by Master [11] (8 per cent), Mullins [8] (9 per cent) and Conner and Holt [6e] (16.2 per cent) and the higher mortality rates found by Cooksey [12] (39.6 per cent), Howard [9a] (24 per cent), Rosenbaum and Levine [4] (33 per cent) and Levine and Brown [6c] (53 per cent). Analysis of our series shows that the immediate mortality rate increases with age, is greater with the second than with the first attack and is higher in those with a history of preexisting cardiac disease.

TABLE 2.—*Immediate Mortality from Recent Myocardial Infarction*

	Number of Cases	Percentage of Series	Average Age, Yr.	Number of Deaths	Mortality, %
Total	572	....	61.5	125	21.8
Men	392	68.5	59.6	73	18.6
Women	180	31.5	63.4	52	28.9

SEASONAL INCIDENCE

The seasonal incidence of myocardial infarction was discussed in 1926 by Bundesen and Falk [13] and in 1927 by Cohn.[14] Since then, numerous reports have appeared, all pointing to a lower incidence in summer. Master and associates [15] did not consider that the difference in

10. Coombs, C. F.: Observations on the Etiological Correspondence Between Anginal Pain and Cardiac Infarction, Quart. J. Med. **23**:233, 1930.

11. Master, A. M.; Jaffe, H. L., and Dack, S.: The Treatment and Immediate Prognosis of Coronary Artery Thrombosis (Two Hundred and Sixty-Seven Attacks), Am. Heart J. **12**:549, 1936.

12. Cooksey, W. B.: Coronary Thrombosis: Follow-Up Studies with Special Reference to Prognosis, J. A. M. A. **104**:2063 (June 8) 1935.

13. Bundesen, H. N., and Falk, I. S.: Low Temperature, High Barometer and Sudden Death, J. A. M. A. **87**:1987 (Dec. 11) 1926.

14. Cohn, A. E.: Heart Disease from the Point of View of Public Health, Am. Heart J. **2**:275 and 386, 1927.

15. Master, A. M.; Dack, S., and Jaffe, H. L.: Factors and Events Associated with the Onset of Coronary Artery Thrombosis, J. A. M. A. **109**:546 (Aug. 21) 1937.

incidence which they observed was significant. Rosahn,[16] recalculating Master's data, insisted that the difference was significant. Wolff and White[17] and White,[6a] reporting from Boston, observed that in most of their cases the condition occurred in the winter months. Wood and Hedley,[18] reporting from Philadelphia, found a lower incidence in spring and summer than in the autumn and winter; they did not consider that this was due entirely to the fact that this was the season of summer vacations. Mullins,[8] reporting from Pittsburgh, found about twice as many attacks during December, January and February as in the summer months. Bean,[3] reporting from Boston, noted a low incidence in the summer and a slightly greater incidence in the spring than in the winter. Bean and Mills,[19] reporting from Cincinnati, found the same decline in the summer months.

The data in our series are presented in table 3. It will be seen that there is a slight tendency for more attacks to occur in the winter

TABLE 3.—*Seasonal Incidence of Recent Myocardial Infarction*

Year	Jan.	Feb.	March	April	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	Totals
1940	4	3	2	1	7	8	2	5	7	5	8	9	61
1941	13	11	10	10	8	7	5	6	9	7	6	7	99
1942	4	7	8	9	4	7	7	4	7	13	8	5	83
1943	8	7	3	7	7	11	8	8	9	2	17	6	93
1944	6	8	12	8	11	8	9	10	13	12	13	12	122
1945	12	9	7	7	6	6	10	12	10	12	9	14	114
Totals	47	45	42	42	43	47	41	45	55	51	61	53	572

months, but the disease in our patients does not follow a definite seasonal trend. There were more attacks in September than in December and January. There were as many attacks in June and August as in January and February. There were about the same number of attacks in March and April as in July. It must be recalled that our series was obtained during the war years, when vacations away from Chicago were rare. It is likely that the seasonal variation reported by others is to a large extent due to summer migration from the large communities on the part of susceptible persons. Seasonal incidence appears to be an unimportant factor as a precipitating cause of acute myocardial infarction.

16. Rosahn, P. D.: Incidence of Coronary Thrombosis in Relation to Climate, J. A. M. A. **109**:1294 (Oct. 16) 1937.

17. Wolff, L., and White, P. D.: Acute Coronary Occlusions: Report of Twenty-Three Autopsied Cases, Boston M. & S. J. **195**:13, 1926.

18. Wood, F. C., and Hedley, O. F.: Seasonal Incidence of Acute Coronary Occlusion in Philadelphia, M. Clin. North America **19**:151, 1935.

19. Bean, W. B., and Mills, C. A.: Coronary Occlusion: Heart Failure and Environmental Temperatures, Am. Heart J. **16**:701, 1938.

PRECIPITATING CAUSES

Considerable controversy has appeared in the literature concerning the precipitating causes of myocardial infarction. Many observers [20] insist that attacks are precipitated by unusual departures from the ordinary habits of the person. Included are unusual physical exertion and strain, overindulgence in sports, overeating, sexual excesses, emotional upsets, dreams and excessive travel. Occasionally, infections and postoperative states may appear as precipitating factors. The highest incidence of specific precipitating causes of myocardial infarction was reported by Rathe [5] (20.8 per cent). Blumgart [21] presented 11 patients of army personnel, varying in age from 26 to 56 years, with acute myocardial infarction consequent to strenuous exercise to which they were not accustomed. Riesman and Harris [22] and Wolff and White,[17] while agreeing that unusual departures from ordinary habits of living as well as infections may precipitate myocardial infarction, emphasized that many attacks occur while the patient is at rest or sitting or lying in bed. Herrick,[23] MacCollum [24] and Levine and Brown [6c] denied that infections are precipitating factors. Parkinson and Bedford,[7] Luten [25] and Master and associates [15] stressed the fact that many persons are aroused from sleep by an attack of myocardial infarction. Phipps [26]

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20. Kahn, M. H.: Etiologic Factors in Angina Pectoris in Private Practice: Analysis of Eighty-Two Cases, Am. J. M. Sc. **172**:195, 1926. Fitzhugh, G., and Hamilton, B. E.: Coronary Occlusion and Fatal Angina Pectoris: Study of Immediate Causes and Prevention, J. A. M. A. **100**:475 (Feb. 18) 1933. Boas, E. P.: Coronary Occlusion as a Delayed Post-Operative Complication, J. Mt. Sinai Hosp. **3**:224, 1937. Campbell, S. B. B.: The Influence of Gall Bladder and Other Infections on the Incidence of Coronary Thrombosis, Brit. Heart J. **1**:781, 1936. Randall, D. S., and Orr, T. G.: Post-Operative Coronary Occlusion, Ann. Surg. **92**:1014, 1930. Menard, O. J., and Hurxthal, L. M.: Painless Coronary Thrombosis as a Post-Operative Complication, S. Clin. North America **11**:395, 1931. Paterson, J. C.: Relation of Physical Exertion and Emotion to Precipitation of Coronary Thrombosis, J. A. M. A. **112**:895 (March 11) 1939. Boas, E. P.: Angina Pectoris and Cardiac Infarction from Trauma or Unusual Effort with Consideration of Certain Medicolegal Aspects, ibid. **112**:1887 (May 13) 1939.

21. Blumgart, H. L.: The Relation of Effort to Attacks of Acute Myocardial Infarction, J. A. M. A. **128**:775 (July 14) 1945.

22. Riesman, D., and Harris, S. E.: Disease of the Coronary Arteries with a Consideration of Data on the Increasing Mortality of Heart Disease, Am. J. M. Sc. **187**:1, 1934.

23. Herrick, J. B.: The Coronary Artery in Health and Disease, Am. Heart J. **6**:589, 1931.

24. MacCollum, W. G., and Cowdry, E. V.: Arteriosclerosis: A Review of the Problem, New York, The Macmillan Company, 1933, p. 361.

25. Luten, D.: Contributory Factors in Coronary Occlusion, Am. Heart J. **7**:36, 1931.

26. Phipps, C.: Contributory Causes of Coronary Thrombosis, J. A. M. A. **106**:761 (March 7) 1936.

doubted the existence of any causal relationship between infections and undue activity and myocardial infarction. The most emphatic exponent of the lack of precipitating causes for myocardial infarction has been Master and his group.[27] They have emphasized this point in several of their publications.

In 50 of our cases (9.5 per cent) a possible precipitating cause was noted in the chart. This information is summarized in table 4. Eight of the patients had a preceding severe emotional trauma; 19 had infections of the upper respiratory tract, ranging from a sore throat, influenza or "head cold" to frank pneumonia. In 13 cases the disease occurred three to ten days postoperatively; 8 patients had histories of severe exertion, viz., straining at stool, effect of an enema, hurrying to an appointment, severe exercise, driving an automobile across country, delivering a speech, sexual intercourse and lifting a heavy object. One patient had upsetting dreams and another a history of an overdose of

TABLE 4.—*Precipitating Causes of Recent Myocardial Infarction* *

	Number	Percentage
Cases in which there were no evident precipitating causes	474	90.5
Cases in which there were precipitating causes		
Severe emotion	8	1.5
Infections of the upper respiratory tract	19	3.6
Postoperative	13	2.5
Severe exertion	8	1.5
Other causes †	2	0.4
Total	50	9.5

* In other cases no information was available.
† In 1 case the condition occurred after an overdosage of insulin; in the other it followed a disturbing dream.

insulin prior to the myocardial infarction. While our results suggest that these factors played a part in precipitating an acute attack, it must be emphasized that the patients were 50 years of age or older and had preexisting evidence of cardiac disease. Apparently a trigger mechanism may be operative in precipitating acute myocardial infarction only with preexisting coronary disease.

Two sources of error in analyzing precipitating factors are present. One is the tendency of persons to seek for some unusual event whenever they become suddenly ill. The other is the fact that in our series we did not have the opportunity to question the patients personally and therefore had to rely on the record of the case. It is possible that had a personal survey been made without leading questions more pre-

27. Master, A. M.; Dack, S., and Jaffe, H. L.: (*a*) The Relation of Various Factors to the Onset of Coronary Artery Thrombosis, J. Mt. Sinai Hosp. **3**:224, 1937; (*b*) The Precipitating Factors of Coronary Artery Occlusion, Indust. Med. **8**:327, 1939; (*c*) The Relation of Effort and Trauma to Acute Coronary Occlusion, ibid. **9**:359, 1940.

cipitating factors might have been revealed or some of the supposed precipitating factors might have turned out to be merely coincidental. Our study, while suggesting that some factors are of significance in precipitating the attack in at least a small proportion of cases, cannot be considered to have finally settled this highly controversial aspect of myocardial infarction. Nevertheless, it must be emphasized that in the vast majority of cases no precipitating cause was found. Apparently, then, recent myocardial infarction often cannot be prevented by the avoidance of undue activity. In planning long term activity of susceptible patients, this should be borne in mind and taboos kept at a minimum commensurate with common sense.

HYPERTENSION

"A preexisting hypertension is probably the most common etiologic factor in the development of myocardial infarction in the majority of cases" (Levine and Brown [6c]). Allan [28] found a greater frequency of hypertension in patients with myocardial infarction than in the general population in the same age groups. The incidence of hypertension among patients with recent myocardial infarction is reported to vary between 28 per cent (Howard [9a]) and 69 per cent (Master and associates [29]). Thus, Parkinson and Bedford [7] reported 49 per cent, Conner and Holt [6e] 33.9 per cent, Levine and Brown [6c] 40 per cent, Rosenbaum and Levine [4] 57 per cent, Master and associates 62.4 per cent [9f] and 66 per cent,[11] White and Bland [6b] 34 per cent, Bean [3] 49.3 per cent, Fisher and Zuckerman [6j] 65.5 per cent, Smith and associates [6k] 41 per cent and Rathe [5] 63 per cent.

In our series a person was considered to be hypertensive if a definite history of hypertension was found recorded in his chart or was ascertained from his physician or if the patient had a persistent diastolic pressure of over 90 mm. of mercury during his stay in the hospital. In the majority the disease was diagnosed on the latter basis. There were 188 hypertensive patients, or 35.9 per cent, in our series (table 5). Among these, 28 had diabetes mellitus in addition. Our incidence may be lower than that reported by others because we excluded systolic hypertension unaccompanied by diastolic hypertension.

Hypertension occurred more often in the women (49.4 per cent) than in the men (29.7 per cent). This has been observed previously by others. The average age of the hypertensive patients was similar to that of the entire group. The immediate mortality rate of the hyper-

28. Allan, W.: The Relation of Arterial Hypertension to Angina Pectoris and Coronary Occlusion, South. Med. & Surg. **96**:377, 1934.

29. Master, A. M.; Jaffe, H. L.; Dack, S., and Silver, N.: The Course of the Blood Pressure Before, During and After Coronary Occlusion, Am. Heart J. **26**:92, 1943.

tensive group (table 5) corresponds closely to that of the entire series, and this is true of the mortality rates in the two sexes. Our findings suggest that hypertension has no influence on the immediate mortality in myocardial infarction. This is in agreement with the observations of many others [30] except those of Rosenbaum and Levine,[4] who reported a 12 per cent greater mortality rate for their hypertensive than for their normotensive patients.

In agreement with Glendy, Levine and White,[31] and Master and associates [6f] we found a low incidence of hypertension in the younger patients (those between 32 and 36 years of age). In the older group, the incidence of hypertension increased with age, especially in the women.

DIABETES MELLITUS

It is well established that coronary sclerosis is common in diabetes mellitus. Nathanson [32] observed coronary sclerosis in 41 of 100 cases of diabetes at necropsy. Joslin [33] found that patients with diabetes of five or

TABLE 5.—*Sex Distribution and Immediate Mortality in Hypertensive Patients with Recent Myocardial Infarction*

	Number	Percentage of Series	Average Age, Yr.	Number of Deaths	Mortality, %
Total	188	35.9	....	43	22.8
Men	107	29.7	59.0	18	16.8
Women	81	49.4	62.2	25	30.8

more years' duration almost always had coronary sclerosis. Many observers [34] have noted the great frequency of myocardial infarction in

30. White.[6a] Levine and Brown.[6c] Conner and Holt.[6e] Master, Dack and Jaffe.[6f] Fisher and Zuckerman.[6j] Vander Veer and Brown.[9b]

31. Glendy, R. E.; Levine, S. A., and White, P. D.: Coronary Disease in Youth, J. A. M. A. **109**:1775 (Nov. 27) 1937.

32. Nathanson, M. H.: Coronary Disease in One Hundred Autopsied Cases, Am. J. M. Sc. **183**:495, 1932.

33. Joslin, E. P.: Arteriosclerosis and Diabetes, Ann. Clin. Med. **5**:1061, 1927.

34. (*a*) Wilder, R. M.: Necropsy Findings in Diabetes, South. M. J. **19**:241, 1926. (*b*) Blotner, H.: Coronary Disease in Diabetes Mellitus, New England J. Med. **203**:709, 1930. (*c*) Root, H. F., and Sharkey, T. P.: Coronary Arteriosclerosis in Diabetes Mellitus, ibid. **215**:605, 1936. (*d*) Rabinowitch, I. M.: Arteriosclerosis in Diabetes, Ann. Int. Med. **8**:1436, 1935. (*e*) Joslin, E. P.; Root, H. F.; White, P. D., and Marble, A.: The Treatment of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1937, p. 398. (*f*) Root, H. F.; Bland, F. E.; Gordon, W. H., and White, P. D.: Coronary Arteriosclerosis in Diabetes Mellitus: A Postmortem Study, J. A. M. A. **113**:*27* (July 1) 1939. (*g*) Enklewitz, M.: Diabetes and Coronary Thrombosis: An Analysis of Cases Which Came to Necropsy, Am. Heart J. **9**:386, 1934. (*h*) Raab, A. P., and Rabinowitz, M. A.: Glycosuria and Hypoglycemia in Coronary Thrombosis, J. A. M. A. **106**:1705 (May 16) 1936,

diabetes. Enklewitz,[34g] Master and associates,[6f] Conner and Holt,[6e] Bean,[3] White and Bland [6b] and Levine and Brown [6c] reported that from 10 to 23.7 per cent of patients with acute myocardial infarction had diabetes. Levine and Brown [6c] included patients with transient glycosuria in their series. This may explain why their reported incidence was higher than in other series. Master and associates [6f] found that diabetes was commoner in women than in men and that its incidence increased with age. Levine and Brown [6c] concluded that diabetes did not alter the prognosis of the attack or the age at which myocardial infarction occurred. Master and his associates [6f] agreed that diabetes was not a factor in the occurrence of myocardial infarction in men and young women but expressed the opinion that it played a definite part in women over 50 years of age. Conner and Holt [6e] concluded that diabetes in itself is not a predisposing cause of infarction. Saphir and asscoiates [35] found that

TABLE 6.—*Sex Distribution of Recent Myocardial Infarction and Immediate Mortality in Patients with Diabetes with or without Ketosis*

	Number	Average Age, Yr.	Number of Deaths	Mortality, %	Number with Diabetic Ketosis	Number of Deaths with Diabetic Ketosis	Mortality in Patients with Diabetic Ketosis, %
Total	85	....	28	32.9	19	10	52.6
Men	36	59.2	10	27.8	6	2	33.3
Women	49	61.4	18	36.7	13	8	61.5

myocardial infarction was not as frequent in patients with diabetes as might be inferred from the literature.

In our series there were 85 patients with diabetes, or 16.2 per cent of the entire series (table 6). Of these, 28 had hypertension in addition. The average age of the patients with diabetes agreed with that of the whole series. There were 36 men and 49 women. The mortality rate for the men was 27.8 per cent and that for the women 36.7 per cent, as contrasted with 18 and 29 per cent for the whole series. Thus it will be seen that the mortality rate of persons with diabetes is greater than that of the whole group for both the men and the women. In contrast to hypertension, diabetes adds definitely to the gravity of the prognosis. The number of cases of diabetes combined with hypertension is too small for us to draw any specific conclusions about the gravity of this combination. Of the 85 patients with diabetes, 19 (22.4 per cent) had ketosis on their admission to the hospital, and 10 of the 19 died. Twenty-five others (29.4 per cent) were in a poorly controlled

35. Saphir, O.; Priest, W. S.; Hamburger, W. W., and Katz, L. N.: Coronary Arteriosclerosis: Coronary Thrombosis and the Resulting Myocardial Changes, Am. Heart J. **10**:567 and 762, 1935.

diabetic state (the urine contained sugar [3 to 4 plus]). When the number of patients with uncontrolled diabetes and patients with ketosis is subtracted from the entire series of cases of diabetes, the mortality percentage falls within the range for the entire series. Diabetes definitely increases the mortality rate, primarily by leading to uncontrolled diabetic states after infarction. Patients with uncontrolled diabetes therefore require immediate and adequate therapy. As long as there is no ketosis and the fluid balance is maintained, it is perhaps safer not to use insulin. A high blood sugar level provides the optimum nutrition to the myocardium and prevents any dangerous hypoglycemic reactions and also any detrimental direct effect of insulin on the myocardium. More of the women than of the men had diabetes out of control on their admission to the hospital (table 6). It may be concluded from our series that diabetes adds to the gravity of the immediate prognosis, especially in women.

PERIARTERITIS NODOSA AND THROMBOANGIITIS OBLITERANS

On rare occasions, periarteritis nodosa [36] and thromboangiitis obliterans [37] lead to myocardial infarction. One case of periarteritis nodosa and 1 of thromboangiitis obliterans, in both of which the diagnosis was proved at necropsy, are included in our series.

SYPHILIS

Syphilis as an etiologic agent of myocardial infarction has been reported by many.[38] The incidence varies between 2.7 and 14.2 per cent. Levine and Brown [6c] and White [6a] stated that syphilis is a rare underlying factor in the production of myocardial infarction. Cole and Bohning [39] found 3 instances of myocardial infarction in 30 patients with cardiovascular syphilis at necropsy. Syphilis can narrow the coronary ostia and thereby lead to myocardial infarction. However, syphilis is

36. Logue, R. B., and Mullins, F.: Polyarteritis Nodosa: Report of Eleven Cases with a Review of Recent Literature, Ann. Int. Med. **24**:11, 1946.

37. Barron, M. E., and Linenthal, H.: Thromboangiitis Obliterans: General Distribution of the Disease, Arch. Surg. **19**:735 (Oct.) 1929. Samuels, S. S., and Feinberg, S. C.: The Heart in Thromboangiitis Obliterans, Am. Heart J. **6**:255, 1930. Greenfield, I.: Coronary Artery Thrombosis with Recovery in a Case of Thromboangiitis Obliterans, ibid. **22**:707, 1941. Fatherree, T. J., and Hines, E. A.: Vascular Clinics: IV. Fatal Complications of Thromboangiitis Obliterans; a Clinical Study, Proc. Staff Meet., Mayo Clin. **13**:342, 1938. Allen, E. V., and Willius, F. A.: Disease of the Coronary Arteries Associated with Thromboangiitis Obliterans of the Extremities, Ann. Int. Med. **3**:35, 1929.

38. Bean.[3] White.[6a] White and Bland.[6b] Levine and Brown.[6c] Conner and Holt.[6e] Appelbaum and Nicolson.[6g]

39. Cole, S. L., and Bohning, A.: Electrocardiographic Patterns in Cardiovascular Syphilis, Am. J. M. Sc. **207**:317, 1944.

often accompanied by coronary atherosclerosis, and it may be the latter which is responsible for the infarction.

In our series there were 4 possible instances of the disease, with only 2 verified at autopsy. Syphilis is a rare cause of myocardial infarction and was the possible etiologic factor in only 0.8 per cent of our series.

ANGINA PECTORIS

Angina pectoris prior to myocardial infarction has been reported as occurring in from 22.4 to 71.6 per cent of the cases.[40] In our series 382 patients, or 72.9 per cent, had angina pectoris prior to the attack (table 7). Angina pectoris was about equally common in the two sexes and occurred as often in those with anterior as in those with posterior myocardial infarction. The angina was described either as typical or (in 29 cases) as indigestion, stomach ache or heart burn. The mortality rate was 23.3 per cent for the men and 28 per cent for the women,

TABLE 7.—*Relation of Angina Pectoris to Recent Myocardial Infarction and Effect on Immediate Mortality*

	Anginal Attacks Prior to Infarction	No Angina Prior to Infarction	Anginal Attacks During Stay in Hospital Following Infarction	"Silent Coronary" *
Total number	382	138	69	18
Percentage of entire series	72.9	26.3	13.2	3.4
Number of deaths	95	29	27	5
Mortality rate of group, %	25.6	21.0	39.1	27.7

* "Silent coronary" or "silent infarction" is defined as a condition in which no preceding angina or pain occurred during the attack.

both figures only slightly higher than the mortality rate for the entire series. White,[6a] Bedford,[41] Rathe[5] and Fisher and Zuckerman[6j] expressed the opinion that the presence of angina pectoris prior to the attack had no influence on the immediate prognosis of myocardial infarction. Rosenbaum and Levine[4] concluded that the patients with angina pectoris had a better prognosis than those without it. Our results indicate that preexisting angina pectoris had little, if any, effect on the prognosis of recent myocardial infarction.

In 138 patients (26.3 per cent) no attacks of angina pectoris occurred prior to the infarction (table 7). The mortality rate in this group was 21 per cent. The absence of preexisting angina, therefore, does not influence the immediate prognosis of myocardial infarction.

Angina pectoris continued or developed after the infarction while the patient remained in the hospital in 69 cases (13.2 per cent) in our

40. Bean,[8] Rosenbaum and Levine.[4] White.[6a] White and Bland.[6b] Willus.[6d] Conner and Holt.[6e] Parkinson and Bedford.[7] Howard.[9a]

41. Bedford, D. E.: Prognosis in Coronary Thrombosis, Lancet **1**:223, 1935.

series (table 7). These patients remained in the hospital for six to eight weeks (up to ten weeks) and were in bed for the most part. The fact that 27 of these patients died (39.1 per cent) indicates that the persistence or development of angina after infarction makes the immediate prognosis graver. Fisher and Zuckerman [6j] and Master and others [11] found that patients with angina pectoris also had a much poorer prognosis after leaving the hospital, succumbing in many instances because of cardiac failure or another attack of myocardial infarction.

PAIN DURING THE ATTACK OF MYOCARDIAL INFARCTION

Many observers [42] have reported instances in which the patient had no pain before or during the myocardial infarction. This has been called "silent coronary occlusion" or "silent myocardial infarction." The mortality rate among patients with silent infarction has been reported as small. In our series 18 patients had a silent myocardial infarction, with an immediate mortality rate of 27.7 per cent (table 7). This mortality rate is slightly higher than that for the entire series but is of doubtful significance. Saphir and associates [35] found that 13 of their 34 patients had no pain before or during infarction; they observed that congestive failure, debilitating disease or a clouded sensorium may explain the absence of pain in some cases. In our series one third (6 of 18) of the patients with "silent" infarction had congestive cardiac failure. Some observers have stressed that second attacks of myocardial infarction may be painless. In our series all the silent infarctions occurred during initial attacks.

Pain of various descriptions, including pain in the precordium, chest, left arm or epigastrium, occurred in 506 patients in this series at the time of the acute myocardial infarction. For the most part the pain was typical in character and location; but, in 18 patients the pain was atypical, according to its description and location. Some had pain only in the throat, neck, teeth, face, tongue or jaws or in a combination of these. Others had pain in the upper or lower part of the back. Several had pain in the right axilla or in the right half of the chest. Some had pain only in the abdomen and presented a difficult problem in ruling out the diagnosis of an acute surgical condition within the abdomen. One patient had only rectal tenesmus. Of the patients with

42. (*a*) Kennedy, J. A.: The Incidence of Myocardial Infarction Without Pain in Two Hundred Autopsied Cases, Am. Heart J. **14**:703, 1937. (*b*) Gross, H., and Engelberg, H.: A Comparison of the Hypertensive and Nonhypertensive Phases Following Coronary Thrombosis, Am. J. M. Sc. **199**:621, 1940. (*c*) Wearn, J. T.: Thrombosis of Coronary Arteries with Infarction of the Heart, ibid. **165**:250, 1923. (*d*) Gorham, L. W., and Martin, S. J.: Coronary Occlusion With and Without Pain: An Analysis of One Hundred Autopsied Cases with Reference to the Tension Factor in Cardiac Pain, Arch. Int. Med. **62**:821 (Nov.) 1938.

atypical pain, 4 died (22.2 per cent), which corresponds to the mortality rate for the entire series.

The typical pain was described as squeezing, pressure, burning and choking. The duration of pain was extremely variable, lasting anywhere from one to thirty-six hours. Saphir and associates [35] found that the duration and severity of the pain were unreliable guides in the diagnosis of acute myocardial infarction. The character and intensity of the pain, to a large extent, depend on the threshold for pain, and this varies from person to person (Libman [43]). White [6a] stated that the more severe the pain, the worse the prognosis. Rosenbaum and Levine [4] and others observed that the severity of the pain, its location and its radiation had little prognostic value. We agree that the character, location, radiation and duration of the pain during the attack are of no prognostic significance.

BLOOD PRESSURE DURING AND AFTER ACUTE MYOCARDIAL INFARCTION

A fall in blood pressure following myocardial infarction has been reported by many observers.[44] These observers noted that the fall in pressure is greater in hypertensive persons than in the normotensive. In both groups systolic and diastolic pressures are affected, but the drop is greater in the systolic pressure, leading to a reduction in pulse pressure. Master and associates [29] called attention to the grave prognosis indicated when the pulse pressure was lower than 20 mm. of mercury. They also noted that in the majority of the cases the fall was rapid, reaching a minimum in one to three days; occasionally, however, the fall was slower, in some cases occupying one to two weeks. They emphasized that the hypertensive group tolerated the drop in blood pressure better than the normotensive group, even though the drop was greater in the former; in many hypertensive patients the blood pressure after it dropped was still at hypertensive levels. Middleton,[45] Fishberg,[46] Bedford [41] and Rosenbaum and Levine [4] found that when the systolic blood pressure was maintained at 80 mm. of mercury or less for hours and, especially, for days, the outlook became extremely unfavorable. Rathe [5] emphasized that the prognosis was grave if the systolic pressure did not return to 100 mm of mercury within five days. Saphir and

43. Libman, E.: Observation on Individual Sensitiveness to Pain, J. A. M. A. **102**:335 (Feb. 3) 1934.

44. Rosenbaum and Levine.[4] White.[6a] Levine and Brown.[6c] Conner and Holt.[6e] Parkinson and Bedford.[7] Wolff and White.[17] Gross and Engelberg.[42b]

45. Middleton, W. S.: The Prognosis and Treatment of Coronary Occlusion, Minnesota M. J. **18**:710, 1935.

46. Fishberg, A. M.: Heart Failure, ed. 2, Philadelphia, Lea & Febiger, 1940, p. 456.

associates,[35] Fishberg [46] and Master and associates [29] observed that occasionally the arterial blood pressure did not fall and at times there was an actual transitory rise.

In our study we observed that the blood pressure usually reached a minimum within twenty-four hours; in some cases, however, the drop continued for one to two weeks. The hypertensive group had a greater drop in blood pressure than the normotensive. The fall in diastolic pressure was less than in systolic. The diminished pulse pressure in itself proved of no prognostic significance unless it became 25 mm. of mercury or less. With such a small pulse pressure there was at least a 50 per cent mortality rate in our series. This is in accord with similar observations reported by Coombs.[10] The degree of fall of systolic blood pressure, provided the pressure remained above 100 mm. of mercury, was of no prognostic significance. When the systolic blood pressure fell below 100 mm. of mercury in the hypertensive group and remained at these levels for three to five days, the prognosis was graver. We observed, further, that when the systolic blood pressure in any group was maintained at less than 90 mm. of mercury for several days the prognosis became extremely grave indeed.

Some of the hypertensive group continued to remain at the hypertensive level, although many had a drop in blood pressure. Actually we had information that a small number of patients in our series had a transitory rise in blood pressure at the time of the myocardial infarction. The cause for this temporary rise in blood pressure remains unanswered. Fishberg [46] suggested that it occurs when there is notable left ventricular failure and is a consequence of asphyxia, but many of our patients with temporary rises in blood pressure did not have decided failure of the left side of the heart. Levine and Ernstene [47] considered that pain alone is not the important stimulus for the elevation of blood pressure; we are inclined to agree with them. It is possible that the rise in pressure may be reflex in origin, resulting from stimulation of nerves in the heart, which may follow the infarction. Singer [48] has noted such a rise in pressure on stimulation of the nerves of the coronary vessels in the dog.

We do not agree with Levine and Brown [6c] that the patients who show a pronounced fall in blood pressure with only a slight subsequent rise do best, because in our series many of these patients did poorly and died.

The 308 patients on whom data on blood pressure were available were divided into three groups according to their blood pressure on discharge from the hospital. In the first group we included all those

47. Levine, S. A., and Ernstene, A. C.: Observations on Arterial Blood Pressure During Attack of Angina Pectoris, Am. Heart J. **8**:323, 1933.

48. Singer, R.: Experiments on Pain Sensitiveness of Heart and Large Blood Vessels and Its Relation to Angina Pectoris, Wien. Arch. f. inn. Med. **13**:157, 1926.

who were admitted with a normal blood pressure and whose pressure remained normal during their stay in the hospital. In this group there were 144 patients; 35 of these had a history of hypertension. In the second group were those who were admitted with an elevated blood pressure and whose blood pressure on discharge from the hospital was within normal limits. There were 85 patients in this group, 78 of whom had a history of hypertension. In the third group were the patients who had an increased blood pressure on discharge. In this group there were 79 patients, 75 of whom had a history of hypertension. Thus in our series (table 8) 188 of the 308 patients had a history of hypertension. About three fourths of the patients had a normal blood pressure on discharge from the hospital, although four fifths of them had a definite history of hypertension. The remaining one fourth had hypertension on discharge. Of the known hypertensive patients, 84 (44.7 per cent) had a normal blood pressure on discharge after being hospitalized for an average of six to eight weeks.

TABLE 8.—*Immediate Mortality from Recent Myocardial Infarction in Relation to the Level of the Blood Pressure* *

	Number	Percentage of Entire Series	Number of Deaths	Mortality Rate, %
Hypertensive blood pressure.....	188	35.9	43	22.9
Normotensive blood pressure.....	308	57.8	60	19.8
Shock level of blood pressure.....	36	6.9	28	77.8

* The criteria of separating the groups are discussed in the text.

Levine and Brown [6c] and Master and others [29] observed that shock makes the prognosis worse. In our group of 524 patients, 36 had definite signs, symptoms and blood pressures indicative of shock. Of these, 28 died (table 8). This indicates conclusively that the presence of shock is associated with a poor prognosis. This high mortality rate among the patients in shock (77.8 per cent) contrasts with the mortality rate of 19.8 and 22.9 for the normotensive and the hypertensive group, respectively, not in shock.

The mechanism of the initial fall in blood pressure after infarction is still controversial. Fishberg [46] at first attributed it to peripheral circulatory failure and thought that it was reflex in origin, the reflex originating in the heart. However, Mendlowitz and associates [49] attributed it to forward failure arising dynamically because of the infarction in the left ventricle. The latter viewpoint was later concurred in by Fishberg [46] and by Stead.[50] We also consider that the fall in blood pressure

49. Mendlowitz, M.; Schauer, G., and Gross, L.: Hemodynamic Studies in Experimental Coronary Occlusion: II. Closed Chest Experiment, Am. Heart J. **13**:664, 1937.

50. Stead, E. A., and Ebert, R. V.: Shock Syndrome Produced by Failure of the Heart, Arch. Int. Med. **69**:369 (March) 1942.

is cardiogenic and due to a diminished cardiac output involving forward failure. This viewpoint as to the cardiogenic origin appears to be supported by the observations of Master and associates,[29] who found that around two thirds of the hypertensive patients had a return of their blood pressure to hypertensive levels within one to two years after the occurrence of the infarction.

LOCATION OF INFARCT

Criteria used for localizing infarcts are those established by one of us (L. N. K.).[51] In this series there were 244 infarctions of the anterior and 160 of the posterior wall (table 9). In addition, there were 49 infarctions of the anteroseptal wall, 22 of the anterolateral wall, 34 of

TABLE 9.—*Distribution of Recent Infarction by Location as Determined by Electrocardiographic Contour*

	Total			Men			Women		
Location	No. in Group	No. of Deaths in Group	Immediate Mortality Rate, %	No. in Group	No. of Deaths in Group	Immediate Mortality Rate, %	No. in Group	No. of Deaths in Group	Immediate Mortality Rate, %
Anterior	244	43	17.6	159	28	17.6	85	15	17.6
Anteroseptal	49	20	40.8	36	12	33.0	13	8	61.5
Anterolateral	22	0	0.0	18	0	0.0	4	0	0.0
Posterior	160	37	23.1	110	20	18.2	50	17	34.0
Posteroseptal	34	11	32.3	27	7	25.9	7	4	57.1
Posterolateral	11	0	0.0	8	0	0.0	3	0	0.0
Atypical	26	8	30.8	18	4	22.2	8	4	50.0
Lateral	2	0	0.0	2	0	0.0	0	0	0.0
Combined *	24	6	25.0	14	2	14.3	10	4	40.0
Total	572	125	21.9	392	73	18.6	180	52	28.9

* Indicates posterior pattern in limb leads and anterior pattern in the chest leads.

the posteroseptal wall and 11 of the posterolateral wall. Twenty-six were atypical, 2 were lateral and 24 were combined (a posterior pattern in the limb leads and an anterior pattern in the chest leads). The mortality rate was greatest in the patients having infarcts involving the septum and in those having the atypical and combined varieties.

Vander Veer and Brown,[9b] Stroud[52] and Wood and associates[53] stated the belief that anterior infarction is far more serious than the variety involving the posterior wall. Master and associates,[11] Willius,[6d]

51. Katz, L. N.: Electrocardiography, ed. 2, Philadelphia, Lea & Febiger, 1946, chap. 11, p. 280.

52. Stroud, W. B., in discussion on Levine, S. A., and Levine, H. D.: Electrocardiographic Study of Lead IV, with Special Reference to Findings in Angina Pectoris, Tr. A. Am. Physicians **50**:303, 1935.

53. Wood, F. C.; Bellet, S.; McMillan, T. M., and Wolferth, C. C.: The Electrocardiographic Study of Coronary Occlusion: Further Observations on the Use of the Chest Leads, Arch. Int. Med. **52**:752 (Nov.) 1933.

Barnes and Ball [54] and Levine and Brown [6c] concluded that the mortality rate is the same in both anterior and posterior varieties. In our series we found the mortality rate to be 17.6 per cent among the patients with infarctions of the anterior wall and 23.1 per cent among those with infarctions of the posterior wall. The former is slightly below and the latter slightly above the average mortality rate. In all varieties except that involving the anterior wall the mortality rate was higher in the women than in the men. It would appear that there is little difference, by and large, in the immediate mortality rate among patients with infarctions of the anterior wall and those with infarctions of the posterior wall.

CARDIAC ARRHYTHMIA

In the consideration of cardiac arrhythmias we have excluded sinus tachycardia and intraventricular block from the general consideration. These will be considered separately in the following paragraphs.

Cardiac arrhythmias have been reported [55] to occur in myocardial infarctions in 9 to 27 per cent of the cases, with an average of 18 per cent. The most common arrhythmia reported was premature systoles of ventricular origin. These did not influence the immediate prognosis of myocardial infarction. Next in order of frequency was auricular fibrillation, with heart block and paroxysmal tachycardia following. Master and associates [55a, b] emphasized that arrhythmias are more common in severely ill patients who have previous cardiac damage resulting from hypertension or previous myocardial infarction. Many of these patients in their series had enlarged hearts. They found that arrhythmias were more prone to develop in women than in men and that the frequency increased with age. Several observers have emphasized that persistence of an arrhythmia for any considerable period may be followed by cardiac failure. It has been noted that some arrhythmias seem to initiate myocardial infarction or at least are present at the start.

54. Barnes, A. R., and Ball, R. G.: The Incidence and Situation of Myocardial Infarction in One Thousand Consecutive Postmortem Examinations, Am. J. M. Sc. **183**:215, 1932.

55. (*a*) Master, A. M.; Dack, S., and Jaffe, H. L.: Partial and Complete Heart Block in Acute Coronary Artery Occlusion, Am. J. M. Sc. **196**:513, 1938; (*b*) Disturbances of Rate and Rhythm in Acute Coronary Artery Thrombosis; Ann. Int. Med. **11**:735, 1937. (*c*) Salcedo-Salgar, J., and White, P. D.: The Relationship of Heart Block, Auriculoventricular and Intraventricular to Clinical Manifestations of Coronary Disease, Angina Pectoris and Coronary Thrombosis, Am. Heart J. **10**:1067, 1935. (*d*) Askey, J. M., and Neurath, O.: The Prognostic Significance of Auricular Fibrillation in Association with Myocardial Infarction, ibid. **29**:575, 1945. (*e*) Meakins, J. C., and Eakin, W. W.: Coronary Thrombosis: A Clinical and Pathologic Study, Canad. M. A. J. **26**:18, 1932. (*f*) Schwartz, S. P.: Auriculoventricular Dissociation and Adams-Stokes Syndrome in Acute Coronary Vessel Closure, Am. Heart J. **11**:554, 1936.

Askey and Neurath [55d] and Levine and Brown [6c] observed that auricular fibrillation was the most serious arrhythmia. Appelbaum and Nicolson,[6g] Schwartz,[55f] Master and associates [55a, b] and Rosenbaum and Levine [4] stated the belief that heart block was the most serious. Master and associates [55b] observed that most arrhythmias occurred in the first few days and were often transient. They emphasized that auricular fibrillation and paroxysmal tachycardia were usually transient, while heart block persisted for a longer time and in some cases became permanent.

In our series there were 94 instances of arrhythmia (16.4 per cent), excluding occasional premature systoles, sinus tachycardia and intra-

TABLE 10.—*Arrhythmias Occurring Following Recent Myocardial Infarction* *

Type of Arrhythmia	Number	Percentage of Series	Number of Deaths During Stay in Hospital	Percentage of Deaths in Group
Auricular fibrillation	17	18.1	5	29.4
Auricular flutter	4	4.3	3	75.0
First degree auriculoventricular block	23	24.5	6	23.1
Second degree auriculoventricular block	11	11.7	6	54.6
Complete auriculoventricular block with idioventricular pacemaker below bundle bifurcation	4	5.3	4	100.0
Complete auriculoventricular block with pacemaker above bundle bifurcation	1		1	
Sinoauricular block	3	3.2	0	0.0
Coronary nodal rhythm	5	5.3	1	20.0
Middle nodal rhythm	2	2.1	1	50.0
Supraventricular tachycardia	3	3.2	2	66.6
Ventricular tachycardia	5	5.3	3	60.0
Runs of auricular extrasystoles	5	5.3	1	20.0
Runs of ventricular extrasystoles	1	1.0	1	100.0
Auriculoventricular dissociation	3	3.2	2	66.6
Ventricular extrasystoles from two foci	1	1.0	1	100.0
Ventricular extrasystoles in pairs	1	1.0	0	0.0
Numerous ventricular extrasystoles	2	2.1	1	50.0
Numerous auricular extrasystoles	5	5.3	3	60.0
Frequent auricular and ventricular extrasystoles	3	3.2	0	0.0
Totals	94	....	41	43.6

* This table does not consider occasional premature systoles, sinus tachycardia or intraventricular block.

ventricular block (table 10). They occurred in 64 men, with an average age of 60.4 years, and in 30 women, with an average age of 68.1 years. Twenty-one of the men (32.8 per cent) and 20 of the women (66.7 per cent) died, a combined mortality rate of 43.6 per cent. Thus it would appear that arrhythmias occurred with equal frequency in both sexes but at a later age in the women and that the prognosis was grave in both sexes but particularly so in the women. Arrhythmia is therefore an extremely grave complication in myocardial infarction.

The most frequent of the arrhythmias was first degree auriculoventricular block, which occurred in 23 patients (24.5 per cent). Next in frequency was auricular fibrillation, which occurred in 17 patients (18.1 per cent). Partial or second degree block occurred in 11 patients (11.7 per cent). Ventricular tachycardia occurred in 5 patients, while

supraventricular tachycardia occurred in 3. Complete heart block occurred in 5 patients, auricular flutter in 4 and nodal rhythm in 7.

Patients with complete heart block or with runs of ventricular premature systoles had the poorest prognosis, with a mortality rate of 100 per cent. Patients with auricular flutter had a mortality rate of 75 per cent; those with supraventricular tachycardia, 66.6 per cent, and those with ventricular tachycardia, 60 per cent. Among patients with auricular fibrillation and first degree auriculoventricular block there was a much lower mortality rate, 29.4 per cent and 23.1 per cent respectively.

Fifty-nine of the 94 patients with arrhythmias received digitalis and/or quinidine, and 41 of them (68.1 per cent) died (table 11). Fifteen of the 30 patients who received digitalis died—a 50 per cent mortality rate. Seven of 17 of the patients who received quinidine died—a mortality rate of 41.2 per cent. Seven of 12 of the patients

TABLE 11.—*Comparison Between Therapy and Immediate Mortality of Patients with Arrhythmia Following Recent Myocardial Infarction*

	Number in Group	Number of Deaths in Group	Mortality Rate of Group, %
Untreated	35	12	34.3
Treated			
With digitalis alone	30	15	*50.0
With quinidine alone	17	7	41.2
With both digitalis and quinidine	12	7	58.3
Total treated	59	29	49.2

who received both digitalis and quinidine died—a mortality rate of 58.2 per cent. Thirty-five of the 94 patients received no treatment, and 12 (34.3 per cent) died. Our results show no reduction in immediate mortality rate following the use of digitalis and quinidine; in fact, the mortality rate is apparently increased. The results support the contention of Master and associates [55b] that quinidine and/or digitalis therapy of arrhythmias in myocardial infarction is dangerous, more so than the presence of an arrhythmia alone. The reason that so many of the patients received digitalis and/or quinidine was because they had cardiac failure besides the arrhythmia and it was felt that the arrhythmia contributed to the cardiac failure or at least was detrimental and so should be abolished. The influence of cardiac failure in itself on prognosis will be considered in the following text.

In our series there were 73 cases of occasional premature systoles (table 12), a lower frequency than is reported by other observers.[56] In 44 they were ventricular, in 26 they were auricular and in 3 they

56. Levine and Brown.[6c] Master and associates.[55b]

were nodal. There were 11 deaths (25 per cent) among the patients with the ventricular variety, 6 among those with the auricular variety (23.1 per cent) and no deaths among those with the nodal premature systoles. The average rate of death among patients with all varieties of premature systoles was 16.6 per cent for the men and 34.6 per cent for the women. These figures compare favorably with the mortality rate for the entire series. Apparently premature systoles when occurring occasionally are tolerated well by patients with myocardial infarction, at least as far as immediate mortality is concerned. By contrast,

TABLE 12.—*Sex Distribution and Immediate Mortality Rate of Patients with Occasional Premature Systoles Following Recent Myocardial Infarction*

	Group			Men			Women		
Type	Number	Deaths	Mortality Rate, %	Number	Deaths	Mortality Rate, %	Number	Deaths	Mortality Rate, %
Ventricular	44	11	25.0	31	6	19.3	13	5	38.4
Auricular	26	6	23.1	14	2	14.2	12	4	33.3
Nodal	3	0	0.0	2	0	0.0	1	0	0.0
Total	73	17	23.3	47	8	16.6	26	9	34.6

TABLE 13.—*Occurrence of Intraventricular Block with Recent Myocardial Infarction*

						Location of Infarct				No. in Group with		
Sex	No. in Group	Average Age, of Group, Yr.	No. of Deaths in Group	Immediate Mortality Rate of Group, %	No. That Were Transitory	Anterior	Posterior	Atypical	Combined	Cardiac Failure	Hypertension	Both Hypertension and Cardiac Failure
Male	53	62.3	17	32.1	8	31	20	1	1	25	21	8
Female	19	61.3	10	52.6	3	8	9	1	1	12	7	5
Total	72	....	27	37.5	11	39	29	2	2	37	28	13

as pointed out previously, patients with runs of premature ventricular systoles had a mortality rate of 100 per cent.

INTRAVENTRICULAR BLOCK

Master and associates [57] observed that intraventricular block is usually evidence of severe cardiac disease. Patients with intraventricular block may have enlarged hearts, hypertension, previous myocardial infarcts and, frequently, heart failure. Master and his colleagues stressed the fact that intraventricular block is usually permanent and significant of septal involvement. In our series there were 72 cases of intra-

57. Master, A. M.; Dack, S., and Jaffe, H. L.: Bundle Branch and Intraventricular Block in Acute Coronary Artery Occlusion, Am. Heart J. **16**:283, 1938.

ventricular block (table 13), or 12.5 per cent. It was found in all types of location of myocardial infarction. Fifty-three of the patients were men and 19 were women. Among the men there were 17 deaths (32.1 per cent) and among the women 10 deaths (52.6 per cent). Intraventricular block, therefore, increases the gravity of the prognosis. The block was transient in 11 instances.

Of the 72 patients with intraventricular block, 37 (51.4 per cent) had congestive heart failure, 28 (38.9 per cent) had hypertension and 13 (18.1 per cent) had both congestive heart failure and hypertension. The patients with persistent intraventricular block were those who were severely ill and had a history of either previous infarction or enlarged hearts with heart failure and hypertension. Our observations are in accord with those of Master and associates.[57]

CONGESTIVE HEART FAILURE

Many observers [58] found that patients with myocardial infarction may exhibit signs and symptoms of congestive heart failure at the onset of the attack or during the first few days. Reports [46] have also appeared of the occasional occurrence of acute pulmonary edema or of sudden aggravation of preexisting heart failure as the only indication of myocardial infarction, particularly in Negroes.[59] In such patients there is usually reported to be some form of preexisting cardiac damage, due to hypertension, previous myocardial infarction or coronary sclerosis. Myocardial infarction involving a large area of the heart has been reported to be invariably accompanied with congestive heart failure. The incidence of congestive heart failure is found to increase with age. Master and associates [58] noted that congestive heart failure occurred with the same frequency in both sexes, but Rosenbaum and Levine [4] found it to be slightly more common in women. Master and associates [58] and Levine and Brown [6c] noted that three quarters of the patients with sinus tachycardia had congestive heart failure. As mentioned before, a prolonged arrhythmia can produce or aggravate congestive heart failure. Gross and Engelberg [42b] reported a high incidence of congestive heart failure in their series (90 of 100 cases), but most observers have found a lower incidence than this. Fishberg,[46] Harrison [60] and Master and associates [58] observed that many patients with congestive cardiac failure associated with recent myocardial infarction are also in shock and

58. Master, A. M.; Dack, S., and Jaffe, H. L.: Coronary Thrombosis: An Investigation of Heart Failure and Other Factors in Its Course and Prognosis, Am. Heart J. **13**:330, 1937. See this reference for literature.

59. Hunter, W. S.: Coronary Occlusion in Negroes, J. A. M. A. **131**:12 (May 4) 1946.

60. Harrison, T. R.: Failure of the Circulation, Baltimore, Williams & Wilkins Company, 1935, pp. 316 and 328.

that in fatal cases the congestive failure usually predominates, except when death occurs early; in the latter instance shock predominates. All observers agree that congestive heart failure is of grave prognostic significance in patients with myocardial infarction.

In our series there were 121 instances (23.1 per cent) of congestive heart failure (table 14), usually of left-sided or combined heart failure. There were 65 men, or 17 per cent, with an average age of 61.3 years, and 56 women, or 31 per cent, with an average age of 69.1 years. Of the 65 men, 30 died (46.2 per cent), while 21 of the 56 women died (37.5 per cent), with an immediate mortality rate of 41.9 per cent for both sexes. The age of the men with congestive failure corresponds with that of the entire series, but the age of the women with failure is distinctly higher than the average for the women in the entire series. The frequency of congestive heart failure was greater in the women

TABLE 14.—*Immediate Mortality Rate in Congestive Heart Failure Complicating Recent Myocardial Infarction*

Sex	Number in Group	Average Age of Group, Yr.	Number of Deaths in Group	Mortality Rate of Group, %
Male	65	61.3	30	46.2
Female	56	69.1	21	37.5
Total	121	....	51	41.9
Without digitalis	20	....	4	20.0
With digitalis	101	....	47	46.5

than in the men. Our results confirm the impression that congestive failure is an extremely grave sign in both men and women but especially so in men. This is not unexpected, since the ordinary active older man has a greater level of activity than the ordinary active older woman. Rest in a man, therefore, is a greater departure from ordinary activity. Hence, when failure occurs when he is at rest it might be more ominous.

SINUS TACHYCARDIA

Sinus tachycardia in acute myocardial infarction has been stressed by some observers as a grave sign.[61] In our series 116 patients (20.3 per cent) had sinus tachycardia (viz., a ventricular rate of over 100 in the first electrocardiogram—table 15). Of these, 79 were men, with an average age of 59.3 years, and 37 were women, with an average age of 62.4 years. Of these 116 patients, 65 died—a mortality rate of 57.1 per cent. Forty of the deaths occurred in men (50.6 per cent),

61. Levine and Brown.[6c] Master and associates.[58]

and 25 occurred in women (67.6 per cent). It is obvious, therefore, that sinus tachycardia is an exceedingly grave prognostic sign in both sexes.

Of the 116 patients with sinus tachycardia, 56 (48.2 per cent) had congestive heart failure, and 40 of the 56 died (71.4 per cent). The combination of tachycardia and congestive failure is of graver prognostic significance than either alone.

DIGITALIS IN CONGESTIVE HEART FAILURE

Of the 121 patients with heart failure, 101 received digitalis (table 14). Forty-seven of these patients died (a mortality rate of 46.5 per cent). Of the 20 patients with congestive heart failure who did not receive digitalis, only 4, or 20 per cent, died—a rate in agreement with the mortality rate in the entire series. It would appear from our observations that digitalis may be harmful when given to a patient with an acute myocardial infarct who has cardiac failure. As pointed out by Master and associates,[58] many of these patients are in

TABLE 15.—*Immediate Mortality Rate in Recent Myocardial Infarction Complicated by Sinus Tachycardia* *

Sex	Number in Group	Average Age of Group, in Years	Number of Deaths in Group	Mortality Rate in Group, %
Male	79	59.3	40	50.6
Female	37	62.4	25	67.6
Total	116	....	65	57.1

* Determined by a sinus rate over 100 in the first electrocardiogram following infarction.

shock, a definite contraindication to the use of digitalis. It is possible that the difference in the mortality incidence attributed to the use of digitalis may be, in part at least, due to the graver state of the patient receiving this drug. Despite the risk, we believe that digitalis should be given when there are clear signs and symptoms of progressive heart failure and that the patients should be digitalized slowly. If acute pulmonary edema is present, the patient should be digitalized more rapidly. The criteria establishing the presence of congestive heart failure consist of persistent dyspnea, cyanosis and, especially, rales in the bases of the lungs. However, the diagnosis of pneumonia, which can give similar signs and symptoms, must be excluded. It is likely that the number of deaths due to myocardial infarction might be greatly decreased if digitalis were not so indiscriminately employed. There is perhaps a tendency to administer digitalis too rapidly in mild, transient and nonprogressive congestive failure. Evidences of forward failure and, especially, the appearance of shock are to be considered definite contraindications to the exhibition of digitalis.

THROMBOEMBOLIC PHENOMENA

Thromboembolic phenomena have been recorded by many observers.[62] Parkinson and Bedford [7] emphasized that involvement of the intraventricular septum in myocardial infarction may cause thrombosis of both ventricles, leading to pulmonary and systemic emboli. Nay and Barnes [62d] observed that the emboli arising from the left side of the heart are found most often in the spleen, kidney and brain and less commonly in the mesenteric vessels and the vessels of the extremities. Blumer [62b] expressed the opinion that some of the arterial occlusions may be the result of thrombosis, coincident with or subsequent to the myocardial infarction. Bean [3] and Rosenbaum and Levine [4] emphasized that most pulmonary emboli arise from veins of the pelvis and the extremities and that pulmonary occlusion, to a lesser extent, may arise from local thrombosis of the pulmonary vessels. Levine and Brown[6c] observed that many instances of hemiplegia are due to emboli arising from the heart following acute myocardial infarction. Dozzi [62c] found that 29 per cent of patients with myocardial infarction had cerebral thrombosis or embolism at necropsy. Askey and Neurath [62e] stressed the fact that emboli may arise in the heart during auricular fibrillation. Garvin,[62f] in a series of autopsies, found that thrombosis of the auricles was a frequent occurrence and may be the source of emboli. Nay and Barnes [62d] noted that the majority of pulmonary emboli occurred when the blood pressure was low and when the patient had enforced rest in bed, with lack of movement of the extremities. These factors contribute to the formation of phlebothrombosis of the extremities, which in turn is the most frequent cause of pulmonary emboli. All observers agreed that emboli and thrombotic phenomena were of grave prognostic significance in patients with acute myocardial infarction.

In our series there were 52 patients (9.9 per cent) with embolic and thrombotic phenomena (table 16), and 29 of these patients died, a mor-

62. (*a*) Harrington, A. W., and Wright, J. H.: Cardiac Infarction: A Study of One Hundred and Forty-Eight Cases, Glasgow M. J. **119**:1, 1933. (*b*) Blumer, G.: The Importance of Embolism as a Complication of Cardiac Infarction, Ann. Int. Med. **11**:499, 1937. (*c*) Dozzi, D. L.: Cerebral Embolism as a Complication of Coronary Thrombosis, Am. J. M. Sc. **194**:824, 1937. (*d*) Nay, R. M., and Barnes, A. R.: Incidence of Embolic or Thrombotic Processes During the Immediate Convalescence from Acute Myocardial Infarction, Am. Heart J. **30**:65, 1945. (*e*) Askey, J. M., and Neurath, O.: The Treatment of Auricular Fibrillation Occurring with Myocardial Infarction, ibid. **30**:253, 1945. (*f*) Garvin, C. F.: Infarction in Heart Disease, Am. J. M. Sc. **203**:473, 1942. (*g*) Macht, D. I.: Experimental Studies on Heparin and Its Influence on Toxicity of Digitaloids, Congo Red, Cobra Venom and Other Drugs, Ann. Int. Med. **18**:772, 1943. (*h*) de Takats, G.; Trump, R. A., and Gilbert, N. C.: The Effect of Digitalis on the Clotting Mechanism, J. A. M. A. **125**:840, 1944. (*i*) Massie, E.; Stillerman, H. G.; Wright, C. S., and Minnick, V.: Effect of Digitalis Administration on the Coagulability of Human Blood, Proc. Central Soc. Clin. Research **16**:45, 1943.

tality rate of 55.8 per cent. There were 26 instances of pulmonary emboli, with 14 deaths (53.8 per cent). There were 11 instances of cerebral emboli, with 9 deaths (81.8 per cent). Two patients had both cerebral and pulmonary emboli, and they died. There was only 1 patient who had a fatal mesenteric thrombosis. The remainder had various peripheral emboli involving the lower extremities, kidneys and spleen. There was 1 instance of thrombophlebitis and 1 of recognized phlebothrombosis with pulmonary emboli; both of the patients survived. Our experience, in agreement with that of others, indicates that throm-

TABLE 16.—*Location of Thromboembolic Phenomena Following Recent Myocardial Infarction and Immediate Mortality Rate*

Location	Number in Group	Number of Deaths in Group	Percentage of Deaths in Group
Pulmonary	26	14	53.8
Cerebral	11	9	81.8
Cerebral and pulmonary	2	2	100.0
Femoral	3	1	33.3
Iliac	1	0	0.0
Popliteal	2	1	50.0
Renal	1	0	0.0
Pulmonary and renal	1	0	0.0
Splenic and pulmonary	1	0	0.0
Splenic and renal	1	1	100.0
Mesenteric	1	1	100.0
Thrombophlebitis of leg	1	0	0.0
Pulmonary and popliteal phlebothrombosis	1	0	0.0
Total	52	29	55.8

TABLE 17.—*Immediate Mortality Rate of Patients with Thromboembolic Phenomena Complicating Recent Myocardial Infarction with and without Digitalis Therapy*

	Number in Group	Number of Deaths in Group	Mortality Rate in Group, %
Total	52	29	55.8
Receiving digitalis	20	16	80.0
Not receiving digitalis	32	13	40.6

boembolic phenomena occurring during recent myocardial infarction are of grave prognostic significance in both sexes. Cerebral and pulmonary emboli were the most dangerous.

Of the patients who had thromboembolic phenomena, 20 received digitalis. Sixteen of these died—a mortality rate of 80 per cent (table 17). Of the 32 other patients who received no digitalis, 13 died —a mortality rate of 40.6 per cent. It is thus apparent from our results that the occurrence of thromboembolic phenomena in patients receiving digitalis is more serious than in those without such medication. In part, this may be due to the fact that the treated patients were the more seriously ill. It is possible that the use of digitalis may actually help

to bring about thrombosis and emboli. Macht,[62g] in assaying the use of digitalis in cats, found that it shortened the coagulation time. This effect was also found with ouabain. He concluded that under certain conditions digitalis promotes intravascular clotting and predisposes to thromboembolic phenomena. De Takats and others[62h] reported a diminished effect of heparin in both human beings and dogs in the presence of digitalis. This has been confirmed by Massie and his colleagues[62i] but has been questioned by others. We believe that the possibility that the use of digitalis does abbreviate coagulation time has not been excluded. On this account digitalis might be considered a dangerous drug in patients with myocardial infarction, and the indications for its use must therefore be clear in recent myocardial infarction before it is given. The use of heparin to neutralize this apparent tendency should be investigated. The real hazard in the use of digitalis, however, resides in its tendency to lead to ventricular fibrillation, a potential hazard already existing in every case of acute myocardial infarction.

Because of the serious prognosis attached to the occurrence of thromboembolic phenomena in recent myocardial infarction it is imperative that careful observation and good nursing care be employed for all patients prophylactically. Especially, care should be taken to prevent the occurrence of phlebothrombosis in the deep veins of the leg. When these phenomena occur, treatment must be instituted immediately. Ligation of the femoral vein should be considered if the emboli originate in the veins of the lower extremities, and heparin and/or Dicumarol should be given. When the emboli arise higher in the veins of the leg and when the site of origin is not definitely located, ligation of the inferior vena cava may be employed. If cerebral and intra-abdominal emboli occur, anticoagulant therapy must be administered as soon as possible, in addition to other measures. All who receive anticoagulation therapy should have frequent determinations of clotting time when heparin is used, or of prothrombin time when Dicumarol is used. We are not prepared to state that every patient with myocardial infarction should receive prophylactic anticoagulant therapy, as suggested by Peters and others,[63] until such time as this work has been confirmed in a larger series of cases.

PERICARDITIS

Pericarditis complicating acute myocardial infarction has been reported by many observers.[64] It ranged in frequency from 13.8 per

63. Peters, H. R.; Guyther, J. R., and Brambel, E. C.: Dicumarol in Acute Coronary Thrombosis, J. A. M. A. **130**:398 (Feb. 16) 1946.

64. Stewart, C. F., and Turner, K. B.: A Note on Pericardial Involvement in Coronary Thrombosis, Am. Heart J. **15**:232, 1938.

cent (Levine and Brown [6c]) to 48 per cent (Wolff and White [17]). When the process of infarction extends to the visceral pericardium, pericarditis will develop. When this area is small, no friction rub may be audible even though pericarditis is present. A pericardial rub may not be audible when the infarct involves the posterior surface of the heart unless the subepicardial area is large or spreads to the anterior wall. Saphir and associates [35] emphasized that an audible friction rub does not always indicate involvement of the anterior wall since several of their patients showed involvement of the posterior wall. White [6a] observed that pericarditis was found more frequently in patients who died than in those who survived.

In our series, pericarditis was noted clinically in 26 patients. Only in 15 of these was it verified by the electrocardiogram (which is specific only in acute diffuse pericarditis). It is likely that in many other cases the condition was missed on auscultation, because the rub is transitory and ordinarily not loud. Of the 26 patients with pericarditis, 5 died (19.2 per cent). Although our series of cases of pericarditis is small, it suggests that pericarditis is of little prognostic significance in recent myocardial infarction. It is possible, however, that when pericardial involvement is diffuse, suggesting an extensive infarct, it indicates a poor prognosis. In none of our cases was there evidence of pericardial effusion.

PNEUMONIA

Rosenbaum and Levine [4] emphasized that advanced age and forced rest in bed, pulmonary congestion or the use of narcotics may lead to the development of pneumonia. In their series the incidence of pneumonia complicating myocardial infarction was 9 per cent, with a mortality rate of 89 per cent. In our series 52 patients (9.9 per cent) contracted pneumonia, and of these 30 died—a mortality rate of 57.7 per cent. We agree, therefore, with Rosenbaum and Levine that pneumonia is a grave prognostic sign when it complicates acute myocardial infarction. Penicillin should be given as soon as signs and symptoms of pneumonia become apparent.

GLYCOSURIA

Glycosuria has been reported frequently in the literature as a sequela of acute myocardial infarction. Levine and Brown [6c] expressed the belief that it was produced by pain and fear during the acute episodes and was not necessarily indicative of diabetes mellitus. Edelmann [65] thought that myocardial infarction caused latent diabetes to become

65. Edelmann, A.: Ueber die Bedeutung der Glykosurie und Hyperglykämie bei Erkrankungen der Koronaraterien, Wien. klin. Wchnschr. 47:165, 1934.

manifest. Eppinger [66] attributed the glycosuria to the absorption of the products of protein destruction which favored an outpouring of epinephrine. Raab and Rabinowitz [84h] found abnormal dextrose tolerance curves soon after the acute attack of myocardial infarction, which later became normal. They therefore argued that this was opposed to the existence of a latent diabetes.

In our series we found only 10 instances of glycosuria. This low incidence of glycosuria is probably due to the fact that specimens of urine were not available immediately after the attack. Some of our patients were not admitted to the hospital on the day of the attack; some were admitted as late as several days to two weeks afterward. Furthermore, most of the specimens of urine were examined twenty-four to forty-eight hours after the patient's admission. Since glycosuria is a transitory phenomenon, this may account for the small incidence in our series. It is possible to explain the transient glycosuria as a sequel to pain, fear and apprehension, which tend to release epinephrine, or it may be an expression of a poor circulation through the liver; it is known that ischemia of the liver leads to glycosuria. Vogt [67] has shown that glycosuria persisting over several days in the absence of diabetes mellitus may be due to the effect of epinephrine on the adrenal cortex.

OBSERVATIONS AT AUTOPSY

Of the 125 patients who died, necropsy was permitted on 46. Among the unusual conditions noted were cardiac aneurysms (8 cases) occurring either in old or recent myocardial infarcts.[68] Rupture of the heart occurred in 5 patients and was accompanied by a hemopericardium in each instance. In most cases of partial and complete auriculoventricular block complicating myocardial infarction, the infarct was located on the posterior surface of the left ventricle. In only 2 instances, 1 of a partial and 1 of a complete auriculoventricular block, was there involvement of the anterior surface of the left ventricle without involvement of the posterior wall.

Most of the patients with intraventricular block showed evidence of old fibrosis in the septum and of chronic heart disease of arteriosclerotic origin, or else they showed involvement of the septum by the acute myocardial infarction.

The locations of the infarct as shown in the electrocardiograms were in most instances confirmed by autopsy. This has been discussed in

66. Eppinger, H.: Die Coronarthrombose, Wien. klin. Wchnschr. **47**:210, 1934.

67. Vogt, M.: The Effect of Chronic Administration of Adrenaline on the Suprarenal Cortex and the Comparison of This Effect with That of Hexoestrol, J. Physiol. **104**:60, 1945.

68. Dr. Otto Saphir, of the Department of Pathology, permitted us to examine the files of his department.

detail recently by Katz, Feldman and Langendorf.[69] Occasionally postmortem examination revealed evidence of more extensive involvement of the heart than was suspected from the electrocardiogram.

SUMMARY AND CONCLUSIONS

1. A series of 572 cases of recent myocardial infarction observed at the Michael Reese Hospital in the years 1940 to 1945 inclusive has been studied, particularly in regard to the factors involved in causing immediate mortality. The figures for the mortality are based on deaths occurring during the patients' stay in the hospital. Most of the patients were Jews, and a few were Negroes.

2. Acute myocardial infarction occurs less frequently in women than in men. In women the infarction occurs, on the average, four years later than in men. The greatest frequency of infarction in women is in the seventh decade; men have the greatest frequency of infarction in the sixth decade. The women were, on the average, 3.8 years older than the men at the time of death. Women have a greater immediate mortality rate than men. This appears to be due to the greater incidence of diabetes mellitus, thromboembolic phenomena and arrhythmias in women than in men and to their older age at the time of the attack.

3. No definite seasonal incidence was observed. The period of this study covered the war years, when vacations away from Chicago were rare. Seasonal incidence appears to be an unimportant factor in a consideration of the precipitating cause of myocardial infarction.

4. In a small number of cases precipitating factors such as severe emotion, undue exertion, infection and postoperative states are significant in precipitating myocardial infarction. In this series there were such apparent precipitating factors in 9.5 per cent of the cases. In the remaining 90.5 per cent, no apparent precipitating factor was revealed. In the vast majority of cases myocardial infarction develops without undue stress, even occurring when the patient is in bed.

5. Hypertension occurred in 35.9 per cent of this series. The incidence increased with age, especially in the women, and the condition was rare in the younger group. Hypertension appears to have no influence on the immediate prognosis of acute myocardial infarction.

6. Diabetes mellitus, in contrast to hypertension, adds gravity to the immediate prognosis in both sexes, especially in women. It increases the frequency of death by precipitating uncontrolled diabetes and ketosis. Patients with uncontrolled diabetes and ketosis should receive immediate and adequate therapy. As long as there is no ketosis and the balance

69. Katz, L. N.; Feldman, D., and Langendorf, R.: The Diagnostic Value of Electrocardiographic Patterns Based on an Assay of Two Hundred and Sixty-One Additional Autopsied Cases, Proc. Internat. Am. Cardiac Cong., to be published.

of fluid is adequate, it is perhaps wise not to give insulin. A high blood sugar level appears to be advantageous.

7. Periarteritis nodosa, thromboangiitis obliterans and syphilis are rare causes of myocardial infarction.

8. Angina pectoris preceding the acute infarction was equally common in the two sexes. It has no significant effect on the immediate prognosis. The persistence of anginal pain after the acute attack makes the immediate prognosis graver.

9. The character, location, radiation and duration of the pain appear to have no prognostic significance in acute myocardial infarction. Silent infarctions are no more serious than those with pain.

10. The hypertensive group had a greater drop in blood pressure than the normotensive group following the appearance of the acute infarct. The pulse pressure fell in all groups. Pulse pressures of 25 mm. of mercury or less are of grave prognostic significance. The degree of fall of systolic blood pressures, provided the pressure remains above 100 mm. of mercury, is of no immediate significance. In the hypertensive group a fall in blood pressure to below 100 mm. of mercury for three to five days makes the immediate prognosis poor. In any group a blood pressure of 90 mm. of mercury for several days indicates a poor prognosis. The presence of shock in myocardial infarction is indicative of a poor immediate prognosis. A small number of patients actually have a transitory rise in blood pressure at the time of the acute attack. About two thirds of the patients on discharge from the hospital (usually after six to eight weeks) had a normal blood pressure, irrespective of the fact that many of them had a definite history of hypertension preceding the attack. The remaining one third had hypertensive blood pressures on discharge. The majority of these were known hypertensive patients.

11. The immediate mortality rate in patients with acute myocardial infarction was greatest in those having infarcts involving the septum and in those with the atypical and combined varieties. In all types of infarction except that of the anterior wall, the mortality rate was higher in the women than in the men. There were no statistically significant differences in the mortality rate among patients with infarctions of the anterior wall and those with infarctions of the posterior wall.

12. Cardiac arrhythmias occur in both sexes but at a later age in women. The immediate prognosis is grave in both sexes but particularly so in women. Quinidine and/or digitalis therapy for arrhythmias in acute myocardial infarction is not without hazard, the mortality rate being greater than with the arrhythmia alone. Premature systoles when occurring occasionally have no prognostic significance. However, in patients with runs of ventricular premature systoles there was a

mortality rate of 100 per cent. Intraventricular block increases the gravity of the immediate prognosis. Sinus tachycardia is a grave prognostic sign in both sexes.

13. Congestive heart failure is an extremely grave prognostic sign in both sexes, especially in men. The combination of sinus tachycardia and congestive heart failure is of graver prognostic significance than either alone. The age of women with congestive heart failure is distinctly higher than that of men.

14. Digitalis may be harmful when given to patients who have congestive heart failure complicating acute myocardial infarction. Those who received digitalis were sicker patients, and the high figures for mortality with the use of digitalis probably may be due to the graver state of the patient. Digitalis should be given only when there are clearcut signs and symptoms of progressive heart failure, and then the patients should be digitalized slowly. If acute pulmonary edema is present, digitalization should be more rapid. Patients with equivocal congestive heart failure and those with evidence of forward failure, especially the appearance of shock, should not be given digitalis. Digitalis administered prior to or during thromboembolic phenomena increases the immediate mortality rate. Digitalis appears to shorten the coagulation time, and this increases the hazard of its use in patients with acute myocardial infarction. Its real danger, however, is in the risk of inducing ventricular fibrillation.

15. Thromboembolic phenomena occurring during recent myocardial infarction even when digitalis is not exhibited are of grave prognostic significance in both sexes. Pulmonary and cerebral emboli are the most dangerous. On this account, thromboembolic phenomena require immediate treatment and prophylaxis.

16. Pericarditis complicating acute myocardial infarction is of no immediate prognostic significance. Pneumonia is a grave prognostic sign when it complicates acute myocardial infarction; for this reason penicillin should be given promptly when pneumonia appears. Glycosuria in patients without diabetes was infrequent.

17. It is concluded that studies such as this on even larger groups could help to define more clearly the natural history of acute myocardial infarction and reveal the factors which contribute to the determination of the immediate prognosis. The analysis made in this report, when correlated with similar studies in the past, shows definite trends which should be useful in evaluating management and prognosis in acute myocardial infarction.

CARDIAC OUTPUT IN MAN

An Analysis of the Mechanisms Varying the Cardiac Output Based on Recent Clinical Studies

EUGENE A. STEAD Jr., M.D.
DURHAM, N. C.
AND
JAMES V. WARREN, M.D.
ATLANTA, GA.

CURRENT medical teaching regarding the factors controlling the cardiac output is based mainly on the concepts of animal physiology. When applied to man these concepts have of necessity been rather vague and sketchy. The advent of the foreign gas methods,[1] and, more recently, the wider use of the ballistocardiograph [2] and the method of catherization of the right side of the heart [3] now enable clinicians to investigate the output of the heart by actual measurement. The physician may now add knowledge gained from studies on man to that obtained by the physiologists in laboratory work on animals. With the accumulation of these observations, a reevaluation of the factors controlling the cardiac output in human beings appears to be in order. As might be expected, many factors affecting the cardiac output in man, with his intact nervous and circulatory systems, were not apparent in the conventional heart-lung preparation. The pur-

From the Medical Service of the Grady Hospital and the Department of Medicine, Emory University School of Medicine, Atlanta, Ga.

1. (*a*) Starr, I., Jr., and Gamble, C. J.: An Improved Method for the Determination of Cardiac Output in Man by Means of Ethyl Iodide, Am. J. Physiol. **87**:450-473 (Dec.) 1928. (*b*) Grollman, A.: The Cardiac Output of Man in Health and Disease, Springfield, Ill., Charles C Thomas, Publisher, 1932.

2. (*a*) Starr, I.; Rawson, A. J.; Schroeder, H. A., and Joseph, N. R.: Studies on the Estimation of Cardiac Output in Man, and of Abnormalities in Cardiac Function, from the Heart's Recoil and the Blood's Impacts: The Ballistocardiogram, Am. J. Physiol. **127**:1-28 (Aug.) 1939. (*b*) Nickerson, J. L., and Curtis, H. J.: The Design of the Ballistocardiograph, ibid. **142**:1-11 (Aug.) 1944.

3. (*a*) Cournand, A.; Riley, R. L.; Breed, W. S.; Baldwin, E. de F., and Richards, D. W., Jr.: The Measurement of Cardiac Output in Man Using the Technic of Catheterization of the Right Auricle or Ventricle, J. Clin. Investigation **24**:106-116 (Jan.) 1945. (*b*) McMichael, J., and Sharpey-Schafer, E. P.: Cardiac Output in Man by a Direct Fick Method, Brit. Heart J. **6**:33-40 (Jan.) 1944. (*c*) Stead, E. A., Jr.; Warren, J. V.; Merrill, A. J., and Brannon, E. S.: The Cardiac Output in Male Subjects as Measured by the Technique of Right Atrial Catheterization: Normal Values with Observations on the Effect of Anxiety and Tilting, J. Clin. Investigation **24**:326-331 (May) 1945.

pose of this paper is to bring together these new data which appear to throw light on the mechanisms controlling the cardiac output in man.

On theoretic consideration, variations in the cardiac output might result from variation either in the heart rate or in the stroke volume. Variations in rate, however, appear to play a relatively minor role. Even patients with complete heart block and a constantly low heart rate are able to carry on a normal amount of activity and vary their cardiac outputs to meet circulatory demands of an active life.

An understanding of the mechanisms controlling the cardiac output, therefore, becomes a matter of discovering the factors determining the size of the stroke volume. A change in stroke volume may be produced either by altering the degree of diastolic filling, or by varying the amount of residual blood left in the ventricle at the end of systole or by a combination of these factors. The degree of ventricular filling theoretically could be changed by alteration in the filling pressure (atrial pressure) or by variations in the degree of diastolic relaxation of the ventricles. Changes in the completeness of ventricular emptying could cause considerable change in stroke volume.

METHODS

It is not the purpose of this communication to discuss the validity of the several methods of determining the cardiac output in man. This problem has recently been reviewed by Hamilton.[4] In all the original observations reported here the cardiac output was determined by the method of catheterization of the right side of the heart, the direct Fick principle being utilized, or by the ballistocardiograph. Although the underlying principles of the former method are subject to little criticism, there are many practical problems associated with the technic which may lead to rather large errors in any single determination. In an analysis of some of these difficulties as experienced in over five hundred catheterizations in this clinic, it was concluded that the errors tended to be random and not systematic.[5] A single determination of cardiac output might, therefore, be erroneous, but the results of a series of observations were much less likely to lead to faulty conclusions.

The critically damped, low frequency ballistocardiograph was used in some of the studies reported here.[6] The ballistic method is particularly useful in the study of rapid variations in the cardiac output. In addition, observations may be made many times on the same subjects. Calculation of the cardiac output from the ballistic tracing is based on the results of a comparative study of this method

4. Hamilton, W. F.: Notes on the Development of the Physiology of Cardiac Output, Federation Proc. **4**:183-195 (June) 1944.

5. Warren, J. V.; Stead, E. A., Jr., and Brannon, E. S.: The Cardiac Output in Man: A Study of Some of the Errors in the Method of Right Heart Catheterization, Am. J. Physiol. **145**:458-464 (Feb.) 1946.

6. Nickerson, J. L.; Warren, J. V., and Brannon, E. S.: The Cardiac Output in Man: Studies with the Low Frequency, Critically Damped Ballistocardiograph and the Method of Right Atrial Catheterization, J. Clin. Investigation, to be published. Nickerson and Curtis.[2b]

and the catheter technic carried out in this laboratory. The derivation of the method of calculating the cardiac output is based on certain theoretic assumptions. Regardless of the validity of these assumptions, empirically the final value obtained from a large series of observations showed satisfactory correlation with almost simultaneous determinations of the cardiac output by the catheter method. The two methods are used to supplement each other, each being useful in particular types of circumstances. The catheter technic, in addition to its value in determining the cardiac output, is useful in measuring the pressures in the chambers of the right side of the heart.

In the following discussion the term cardiac output refers to the minute output of the heart. In all the instances discussed here the stroke volume varied in the same direction as did the minute output. To facilitate comparison of values for cardiac output in persons of different size, the cardiac index is used. This is the output per minute per square meter of body surface.

The left atrial pressure was not recorded. Observations from experiments on animals indicate that the left atrial pressure usually parallels that of the right atrium unless cardiac failure occurs.

EFFECT OF VARYING THE FILLING PRESSURE OF THE VENTRICLES

The work of Starling and his colleagues [7] has emphasized the effect of venous inflow on the cardiac output. In the heart-lung preparation they observed that the output of the heart was equal to and determined by the amount of blood flowing into the heart and could increase or diminish within wide limits according to the inflow. The greatest output was obtained by increasing the venous inflow until the atrial pressure was moderately elevated. The output of the heart in the usual heart-lung preparation is considerably less than that present in the resting unanesthetized animal.[8] The maximum output obtained by raising the venous pressure above the normal level is less than the output in the normal dog with a much lower venous pressure.[9] Starling's experiments demonstrated that there was a relation between the diastolic volume of the ventricles and the energy set free in the following systole. He concluded: "The law of the heart is therefore the same as that of skeletal muscle, namely, that the mechanical energy

7. (*a*) Patterson, S. W., and Starling, E. H.: On the Mechanical Factors Which Determine the Output of the Ventricles, J. Physiol. **48**:357-379 (Sept. 8) 1914. (*b*) Patterson, S. W.; Piper, H., and Starling, E. H.: The Regulation of the Heart Beat, ibid. **48**:465-513 (Oct. 23) 1914.

8. (*a*) Gollwitzer-Meier, K.; Kramer, K., and Krüger, E.: Der Gaswechsel des suffizienten und insuffizienten Warmblüterherzens, Arch. f. d. ges. Physiol. **237**:68-92 (Feb. 18) 1936. (*b*) Katz, L. N.; Wise, W., and Jochim, K.: The Dynamics of the Isolated Heart-Lung Preparations of the Dog, Am. J. Physiol. **143**:463-478 (April) 1945. (*c*) Patterson and Starling.[7a]

9. Wiggers, H. C.: Cardiac Output and Total Peripheral Resistance Measurements in Experimental Dogs, Am. J. Physiol. **140**:519-534 (Jan.) 1944. Seligman, A. M.; Frank, H. A., and Fine, J.: Traumatic Shock: XII. Hemodynamic Effects of Alterations of Blood Viscosity in Normal Dogs and in Dogs in Shock, J. Clin. Investigation **25**:1-21 (Jan.) 1946.

set free on passage from the resting to the contracted state depends on the area of 'chemically active surfaces'; i. e., on the length of the muscle fibers." [7a]

While the observation that the output of the heart must depend on its inflow is useful, the experiments of Starling do not elucidate the mechanisms by which the output is increased above the resting level. The maximum output in the preparations studied never reached even the level found in an intact animal of the same size while at rest. It is unusual for the cardiac output in man to fall during the day greatly below the level present under basal conditions. The reserve in the system is in the direction of increasing rather than decreasing the cardiac output. Therefore, one is primarily interested in the means by which the cardiac output is increased above the resting level.

There are several clinical observations which suggest that a change in pressure of the blood in the right atrium is not the primary mechanism by which the normal physiologic variations in cardiac output are produced. The cardiac output of the body at rest is elevated in patients with anemia,[10] thyrotoxicosis,[11] arteriovenous fistula [12] and anxiety.[3c] The right atrial pressure in these conditions is not elevated unless cardiac failure is present. In patients with an arteriovenous fistula in which the lesion is located peripherally, it is possible to determine the right atrial pressure while the cardiac output is lowered by temporarily occluding the fistula with external pressure.[13] The cardiac output returns to its former level on release of the pressure. At these two greatly different levels of cardiac output, the atrial pressure remains unchanged.[14] Similarly when tourniquets obstructing the arterial inflow into the lower extremities of a normal subject are released, the cardiac output rises without a rise in atrial pressure.[15]

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10. Sharpey-Schafer, E. P.: Cardiac Output in Severe Anemia, Clin. Sc. **5**:125-132 (Aug.) 1944. Brannon, E. S.; Merrill, A. J.; Warren, J. V., and Stead, E. A., Jr.: The Cardiac Output in Patients with Chronic Anemia as Measured by the Technique of Right Atrial Catheterization, J. Clin. Investigation **24**:332-336 (May) 1945.

11. Brannon, E. S.; Stead, E. A., Jr., and Warren, J. V.: The Cardiac Output in Thyroid Disease, to be published.

12. Warren, J. V.; Nickerson, J. L., and Elkin, D. C.: The Cardiac Output in Patients with Arteriovenous Fistulas, to be published.

13. Nickerson, J. L.; Elkin, D. C., and Warren, J. V.: The Effect of Temporary Occlusion of Arteriovenous Fistulas on Heart Rate, Stroke Volume, and Cardiac Output, to be published.

14. Warren, J. V.; Cooper, F. W., Jr., and Brannon, E. S.: The Venous and Right Atrial Pressure in Patients with Anteriovenous Fistulas, to be published.

15. Stead, E. A., Jr.; Warren, J. V., and Brannon, E. S.: The Effect of a Large Area of Reactive Hyperemia upon the Cardiac Output and Right Atrial Pressure, to be published.

Administration of certain drugs such as "paredrinol" (2-[2-methylaminopropyl]-phenol) [16] and angiotonin [17] causes a rise in atrial pressure without increasing the cardiac output. Administration of tetraethyl ammonium bromide causes a sharp fall in atrial pressure and a rise in cardiac output.[18]

Additional studies have been carried out in this laboratory to observe the effect of variations of right atrial pressure on the output of the heart. The rapid intravenous administration of isotonic solution of sodium chloride and albumin solutions provided a convenient means of temporarily elevating the right atrial pressure in normal subjects. A rise in atrial pressure of as much as 100 mm. of water produced no constant change in cardiac output.[19] Recently, these observations have been confirmed in another laboratory,[20] although others believe that they have demonstrated a linear relationship between atrial pressure and cardiac output.[21]

In another group of subjects the effect of lowering the atrial pressure was studied.[22] This was carried out either by actually removing 300 to 900 cc. of blood or by pooling a similar amount of blood in the lower extremities by means of tourniquets blocking venous return. In these experiments the atrial pressure was decreased by 30 to 50 mm. of water. The cardiac output at the different levels of venous pressure showed some variation, but there was no consistent relationship to atrial pres-

16. Ranges, H. A., and Bradley, S. E.: Systemic and Renal Circulatory Changes Following the Administration of Adrenin, Ephedrine, and Paredrinol to Normal Men, J. Clin. Investigation **22**:687-693 (Sept.) 1943.

17. Bradley, S. E., and Parker, B.: The Hemodynamic Effects of Angiotonin in Normal Man, J. Clin. Investigation **20**:715-738 (Nov.) 1941.

18. Stead, E. A., Jr.; Warren, J. V.; Hickam, J., and Cargill, W. H.: Unpublished observations.

19. Stead, E. A., Jr.; Brannon, E. S.; Merrill, A. J., and Warren, J. V.: Concentrated Human Albumin in the Treatment of Shock, Arch. Int. Med. **77**: 564-575 (May) 1946. Warren, J. V.; Brannon, E. S.; Weens, H. S., and Stead, E. A., Jr.: The Effect on the Circulation of Normal Subjects of Increasing the Blood Volume and Right Atrial Pressure by Intravenous Infusions, Am. J. Med., to be published.

20. Haynes, B. W., Jr.: The Alterations of Cardiac Output and Plasma Volume in Normal Subjects with the Administration of Concentrated Human Serum Albumin, Proc. Am. Federation Clin. Research **2**:74-75, 1945.

21. (*a*) Barcroft, H.; Edholm, O. G.; McMichael, J., and Sharpey-Schafer, E. P.: Posthaemorrhagic Fainting: Study of Cardiac Output and Forearm Flow, Lancet **1**:489-490 (April 15) 1944. (*b*) Footnote 3 *b*.

22. Warren, J. V.; Brannon, E. S.; Stead, E. A., Jr., and Merrill, A. J.: The Effect of Venesection and the Pooling of Blood in the Extremities on the Atrial Pressure and Cardiac Output in Normal Subjects with Observations on Acute Circulatory Collapse in Three Instances, J Clin. Investigation **24**:337-344 (May) 1945.

sure. Similar experiments, utilizing the ballistocardiograph, in this laboratory [18] and elsewhere [23] failed to show any significant change in cardiac output after moderate loss of blood. Observations from another laboratory did indicate a decline in cardiac output as the atrial pressure was reduced.[8b]

If the blood volume is sufficiently decreased by bleeding, the cardiac output will fall and the circulation become inadequate. Clinically, the state of shock will appear. Once the blood volume has been lowered sufficiently to decrease the cardiac output, observations in human beings parallel those reported for the heart-lung preparation. A small change in atrial pressure then causes a great change in output. Indeed, the change in pressure may be so small that it can hardly be measured by the methods used at the present time. The original observations of Starling on the effect of varying the venous inflow at low levels of cardiac output would lead one to expect this.

An analysis of the conditions existing in patients with atrial septal defect is helpful in understanding the relation between atrial pressure and ventricular output. When the patient is at rest, oxygenated blood flows through the septal defect from the left to the right atrium. This has been repeatedly demonstrated by cardiac catheterization.[24] It is obvious that if flow from one atrium to the other is to occur a difference in pressure of some degree must exist between the two chambers. Since much of the output of the right ventricle returns to the right side of the heart through the defect in the atrial septum, the output of the right ventricle must exceed that of the left ventricle. It is usually assumed that the large amount of blood presented to the right ventricle is the cause of its inordinately large output.

The flow from left to right atrium demonstrates that the mean pressure in the left atrium is greater than that in the right atrium; therefore, it must follow that the right ventricle is filling to a greater degree than the left ventricle, although the right atrial pressure is less than the left atrial pressure. The normal oxygen saturation of the arterial blood usually present in patients without complicating pulmonary disease or pulmonary arterial disease is proof of the fact that the pressure in the right atrium never exceeds that of the left atrium for a sufficient length of time to create an appreciable shunt from right to left. It is fortunate that the relative atrial pressures in these patients may be determined by the direction of the shunt and

23. Shenkin, H. A.; Cheney, R. H.; Govons, S. R.; Hardy, J. D.; Fletcher, A. G., Jr., and Starr I: On Diagnosis of Hemorrhage in Man: Study of Volunteers Bled Large Amounts Am J. M. Sc. **208**:421-436 (Oct.) 1944.

24. Brannon, E. S.; Weens, H. S., and Warren, J. V.: Atrial Septal Defect: Study of Hemodynamics by the Technique of Right Heart Catheterization, Am. J. M. Sc. **210**:480-491 (Oct.) 1945.

do not have to be demonstrated by difficult and delicate mechanical measurements.

In summary, it appears that the level of the right atrial or venous pressure, although important in the heart-lung preparation and in patients with a small blood volume, is not an important factor in determining variations in the output of the heart in normal subjects. In the presence of an adequate blood volume, the resultant atrial pressure is sufficient to meet wide variations in cardiac output. The atrial pressure varies considerably in the normal subject, and the body appears to make no effort to maintain it at constant levels. In the wide variety of conditions studied, a normal differential in pressure between atrium and ventricle was adequate to maintain considerable increases in stroke volume. Other means of altering stroke volume, therefore, must be investigated to explain the observed differences in cardiac output.

CHANGES IN ACTIVITY OF VENTRICLES NOT THE RESULT OF CHANGES IN ATRIAL PRESSURE

On theoretic grounds, the stroke volume could be varied equally well by either of two ways without a change in atrial pressure: (1) by increasing the diastolic volume of the ventricles or (2) by more complete emptying of the ventricles. An increase in stroke volume might be caused by either or by a combination of these mechanisms. Means for distinguishing between these two methods of increasing the stroke volume are not available.

Epinephrine.—Epinephrine has long been recognized by physiologists as acting directly on the myocardium, bringing about increased rate and vigor of contraction.[25] In moderate dosage in human beings it produces an increase in cardiac output.[26] Bradley and Ranges,[16] in studies on two subjects after administration of epinephrine intramuscularly, found that the atrial pressure rose significantly in both. We have studied the effect of small intravenous injections of epinephrine in normal subjects.[18] Increase in the cardiac output occurs early, with little change in atrial pressure. If change occurs at all, there is a slight fall in pressure. This is followed later in most patients by a distinct rise in atrial pressure. Of importance in the present discussion is that the increase in stroke volume occurs without change, or even with a slight fall, in atrial pressure. Records of the pressure in the right ventricle revealed a striking diminution in duration of systole.

Arteriovenous Fistula.—The many vascular injuries of the recent war gave us the opportunity to study the effects of arteriovenous fistulas

25. Best, C. H., and Taylor, N. B.: The Physiological Basis of Medical Practice, ed. 4, Baltimore, Williams & Wilkins Company, 1945.

26. Ranges and Bradley.[16] Stead, Warren, Hickam and Cargill.[18]

on the circulation in a large number of patients. These observations have been reported in detail elsewhere.[27] In the patients with lesions in the extremities the fistula could be rapidly occluded by external pressure. Studies utilizing both the catheter method and the ballistocardiograph have shown that in patients with a large fistula this maneuver is accompanied with a reduction in cardiac output, yet the trial pressure remains unchanged.[14] On release of the pressure, the output returns to its former level. Most interesting, however, are the studies carried out with the ballistocardiograph, showing the speed of this reaction. Several changes take place within the time of one or, at the most, two heart beats. The heart rate slows, the stroke volume decreases and the arterial pressure increases. In many instances the change in arterial pressure is only slight. On release of the pressure, these functions quickly return to their original level. The slowing of the heart is prevented if the patient is given atropine before the fistula is compressed. This gives evidence that the change in heart rate is a reflex response mediated by the vagus nerve. The change in stroke volume occurs despite the use of atropine.

Reactive Hyperemia.—Circulatory phenomena similar to those observed in patients with arteriovenous fistula may be demonstrated in normal subjects.[15] Blood pressure cuffs placed around the legs as high as possible and inflated to 200 mm. of mercury cause only minimal circulatory changes. If the cuffs are left on for fifteen to twenty minutes and then released, a period of so-called reactive hyperemia occurs in the legs. The flow of blood through the area becomes large, so that in certain respects a temporary arteriovenous fistula is formed. This reaction gradually subsides during the next few minutes. The release is accompanied with circulatory changes similar to those observed on release of a compressed arteriovenous fistula. The pulse rate increases, the stroke volume increases, the arterial pressure may fall slightly, but the atrial pressure shows little change. If any is noted, there is a slight fall. Thus, again there is a rapid increase in cardiac output without alteration in filling pressure occurring with such rapidity as to preclude a humoral mechanism.

To be sure that the rise in cardiac output is not due to a large mass of blood returning to the heart without a detectable increase in atrial pressure, the experiment was modified. In addition to the arterial tourniquets, another set was applied at a pressure of 30 mm. of mercury. Care was taken that the legs were emptied of blood by elevating them when the arterial tourniquets were applied. On release of the tourniquets applied at a high pressure, any return flow of blood to the heart was temporarily stopped by the tourniquets applied at a low pressure. Nevertheless, the change in cardiac rate and output occurred as before.

27. Warren, Nickerson and Elkin[12]; footnote 13.

These observations on the effect of epinephrine, arteriovenous fistulas, and reactive hyperemia all demonstrate changes in cardiac output not associated with significant changes in atrial pressure.

The increase in stroke volume with the use of epinephrine seems most likely to be on a humoral basis, the epinephrine acting directly on the ventricle muscle. The increase in cardiac output produced by the opening of an arteriovenous fistula or by reactive hyperemia occurs so rapidly that a humoral mechanism does not appear possible. The increase in cardiac output appears to be related to the opening of an area of low peripheral resistance in the arterial tree.

Assuming that variations in cardiac output may occur in the absence of a change in atrial pressure and that alterations in the stroke volume of the ventricle may be produced by lowering of peripheral resistance, let us examine some of the physiologic and pathologic conditions associated with a modified cardiac output. Anemia and anoxia are two common ones. In both, the amount of blood normally sufficient to supply the needs of the body tissues no longer is able to do so. More blood is needed, and if the cardiovascular system is competent, more is delivered. Studies on patients with severe chronic anemia have revealed that the cardiac output is increased, the peripheral resistance is strikingly diminished and the atrial pressure is normal.[10] It appears possible that the increased cardiac output results from the decreased peripheral resistance just as it does in our subjects with reactive hyperemia. Although far from proved, it is an attractive hypothesis that throughout the body a more or less chronic state of reactive hyperemia exists in order to supply an adequate amount of blood to the tissue. Only by remaining dilated can the peripheral vessels receive, and in turn, deliver to the tissues, an adequate amount of oxygen. A similar mechanism would appear to be operative in anoxia.

Thyrotoxicosis is accompanied with an increase in output of the heart, and, conversely, myxedema is accompanied with a diminished output.[28] Studies by the catheter method have shown that these changes occur in the absence of altered atrial pressure and with relatively normal venous oxygen tension. In other words, the arteriovenous oxygen difference remains relatively normal, the alterations in output varying with the consumption of oxygen. Factors similar to those involved in fever may be operative here, except that the altered requirements of the tissues are the result of a humoral rather than a thermal stimulus.

Anxiety and Exercise.—Psychic factors, as already mentioned, may alter the output of the heart.[3c] Independent of an increase in consumption of oxygen (basal metabolic rate) and pulse rate, the output may be doubled in a person tense and anxious. The atrial pressure is normal.

28. Brannon, Stead and Warren.[11] Grollman.[1b]

The peripheral resistance is greatly lowered, but usually not to a sufficient degree to compensate for the increase in cardiac output. The systolic, diastolic and mean arterial pressures increase, therefore.

Exercise is a potent cause of increased output of the heart.[1b] Here many factors may be involved, such as psychic stimuli, increased metabolic requirements by the tissues and the increased requirements for dissipation of heat. The effect of the increased respiratory movements and increased muscular contraction is not clear. Because of the difficulty in studying the subject during the violent motions of exercise, little is known. The increase in cardiac output by light exercise may occur without a measurable change in right atrial pressure. The peripheral resistance does not usually fall sufficiently to prevent a rise in the arterial pressure from the increase in cardiac output.[18]

The reason for the large output of the right ventricle in patients with an atrial septal defect has not been determined. Since the right ventricle is receiving more blood than the left ventricle in the presence of a lower filling pressure, it is clear that the cause of the increased output of the right ventricle must result from some abnormality in the control of the right ventricular output not dependent on atrial pressure. The increased output of the right ventricle has been found to continue in the presence of striking pulmonary hypertension.[24] This would suggest that the abnormal circulation was not due merely to diminished peripheral resistance in the pulmonary circuit.

POSSIBLE MECHANISMS TO ACCOUNT FOR INCREASE IN CARDIAC OUTPUT PRODUCED BY DECREASE IN PERIPHERAL RESISTANCE

Mechanical Effect From Lowering Peripheral Resistance.—The fall in arterial pressure might increase the stroke volume by mechanically permitting the ventricle to empty more completely. This would assume that residual blood remaining in the ventricles is sufficient to make up the observed increase in systolic output. Although it is not certain whether the normal ventricles empty completely, it appears unlikely that there is a large quantity of residual blood.[29] Westermark [30] has studied the circulation roentgenologically in rabbits by means of moving pictures made during the passage of contrast mediums through the vascular system. Systolic contraction was found to empty the ventricles almost completely while at all times the atria contained considerable blood. In certain pathologic states, however, complete emptying of the ventricles undoubtedly does not occur. Large dilated hearts contain

29. Nylin, G.: On the Amount of, and Changes in, the Residual Blood of the Heart, Am. Heart J. **25**:598-608 (May) 1943.

30. Westermark, N.: On Circulation Through Heart, Big Vessels, and Pulmonary Circulation Simultaneously Recorded by Cinematography, Acta radiol. **23**:473-510 (Oct. 3) 1942.

considerable residual blood.[29] In patients with such hearts the increased stroke volume associated with digitalis therapy is accompanied with a decrease in diastolic volume of the heart.[31] In these circumstances an increased output appears to result from more complete ventricular emptying.

Observations on patients with reflex fainting and postural hypotension demonstrate that a fall in peripheral resistance does not mechanically result in a rise in cardiac output if the autonomic nervous system is not functioning normally. The increases in cardiac output produced by anxiety and by exercise occur with a rise rather than a fall in mean arterial pressure.

Reflex Stimulation of Ventricles.—The immediate change in cardiac output and rate with compression and opening of an arteriovenous fistula is too rapid to be caused by a humoral mechanism. The decided shortening of systole and the rise in right ventricular pressure which are produced by the administration of epinephrine do not occur when the cardiac output is increased by opening an arteriovenous fistula. Both stroke volume and rate change within the space of one beat, and the change is maximal within one or two beats. The change in rate is a vagal reflex inhibited by the administration of atropine. The change in stroke volume is not altered by the use of atropine. It occurs in patients with fistulas of the lower extremity after high spinal anesthesia.

The release of arterial tourniquets likewise causes an immediate rise in cardiac rate and output. The response differs from that obtained on release of an arteriovenous fistula in that the maximal changes in cardiac rate and output do not occur immediately.

It is interesting to speculate on the possibility that the output of the heart in the presence of an adequate volume of blood may be controlled primarily by reflex stimuli acting directly on the ventricles. Afferent stimuli might arise from a lowering of the arterial pressure, from moving muscles, from the emotional content of thought and from many other sources. If such reflexes occur, they are not paralyzed by atropine and have a very short latent period.

Clinical Observations Which Support the Concept That the Cardiac Output is Under Reflex Control.—If reflexes acting on the ventricles were important in the control of the cardiac output, one would expect to find instances in which there was evidence of confusion in the reflexes. Physicians are familiar with the respiratory incoordination in patients with Cheyne-Stokes breathing and with neurocirculatory asthenia. Similar instances of incoordination are found in the circulation.

31. Cohn, A. E., and Steele, J. M.: Studies on the Effect of the Action of Digitalis on the Output of Blood from the Heart: I. The Effect on the Output of the Dog's Heart-Lung Preparations, J. Clin. Investigation **11**:871-895 (Sept.) 1932.

Starr has emphasized this incoordination in patients with neurocirculatory asthenia. In the common faint there is evidence of diffuse overactivity of the autonomic nervous system, with widespread signs of gross incoordination of the reflexes.[32] Despite the presence of the pronounced decrease in peripheral resistance, the cardiac output in these patients does not increase as the arterial pressure falls. If it did, the fall in arterial pressure would not be nearly so profound. It would appear possible that the heart is inappropriately, but reflexly, inhibited from responding normally in this situation.

Persons with postural hypotension likewise display evidence suggestive of abnormal function of the nervous mechanism controlling the heart. Widespread involvement of the autonomic nervous system had been demonstrated in these patients.[33] Frequently the heart rate is relatively fixed and does not increase when the person is standing or after administration of atropine. In these patients the postural fall in arterial pressure is not compensated for by a rise in cardiac output.

CONCLUSIONS

The output of the heart in the presence of an adequate volume of blood is varied by changes in ventricular relaxation and contraction which are independent of fairly wide variations in atrial pressure. The ventricles play an active rather than a passive role in determining the cardiac output. Lowering of the arterial pressure by opening an auriculoventricular fistula or by opening large areas of reactive hyperemia causes an abrupt rise in cardiac output which occurs too rapidly for a humoral mechanism. Anxiety and exercise cause a rise in cardiac output in the presence of an increase in arterial pressure. It is suggested that reflex stimulation of ventricular activity accounts for the changes in cardiac output during daily activity and that the afferent stimuli may arise in part from a lowering of the arterial pressure, the movement of the limbs during exercise and the emotional content of thought. Appreciation of the fact that changes in atrial pressure are not the primary factors in increasing the cardiac output during daily work opens a wide field for investigation.

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32. Warren, Brannon, Stead and Merrill.[22] Barcroft, Edholm, McMichael and Sharpey-Schafer.[21a]

33. Stead, E. A., Jr., and Ebert, R. V.: Postural Hypotension: A Disease of the Sympathetic Nervous System, Arch. Int. Med. **67**:546-562 (March) 1941. Ellis, L. B., and Haynes, F. W.: Postural Hypotension with Particular Reference to Its Occurrence in Diseases of the Central Nervous System, ibid. **58**:773-798 (Nov.) 1936.

SARCOIDOSIS IN SIBLINGS

RAYMOND C. V. ROBINSON, M.D.
AND
RICHARD D. HAHN, M.D.
BALTIMORE

SARCOIDOSIS, or benign lymphogranulomatosis (Besnier-Boeck-Schaumann disease), is now recognized as a relatively common clinical and pathologic entity. In extensive reviews of the subject [1] by various authors the symptoms, clinical course and pathologic findings have been described in detail, so that further comment in this respect is unnecessary.

In spite of the wealth of reports of cases in the literature, only four references to sarcoid in siblings have been found, all from continental Europe. Dressler described Boeck's disease of the lungs in a brother and sister [2] and, in a later paper, in 2 brothers.[3] In all 4 of his cases, the diagnoses were based on the benign course of the disease, roentgenologic findings in the lungs, negative reactions to tuberculin tests (except in 1 case), negative reactions in guinea pigs on inoculation, and inability to find tubercle bacilli on repeated examinations of sputum. Boggild [4] reported probable Boeck's sarcoid of the fingers in sisters 2 and 5 years old. His diagnoses were based solely on the finding of small cystic areas in the bones by roentgenologic examination. Sellei and Berger [5] described a family in which the condition in 5 of 7 siblings

From the Syphilis Division of the Medical Clinic, Johns Hopkins Hospital.

1. Goeckerman, W. H.: Sarcoids and Related Lesions, Arch. Dermat. & Syph. **18**:237 (Aug.) 1928. Thomas, C. C.: Sarcoidosis, Including Fifteen Cases, Twelve in Negroes, ibid. **47**:58 (Jan.) 1943. Longcope, W. T.: Besnier-Boeck-Schaumann Disease: Frank Billings Lecture, J. A. M. A. **117**:1321 (Oct. 18) 1941. Longcope, W. T., and Pierson, J. W.: Boeck's Sarcoid (Sarcoidosis), Bull. Johns Hopkins Hosp. **60**:223 (April) 1937. Reisner, D.: Boeck's Sarcoid and Systemic Sarcoidosis (Besnier-Boeck-Schaumann Disease): Thirty-Five Cases, Am. Rev. Tuberc. **49**:289 (April); 437 (May) 1944.

2. Dressler, M.: Boeck's Disease of Lungs in Siblings: Two Cases, Schweiz. med. Wchnschr. **68**:417 (April 23) 1938.

3. Dressler, M.: Familial Occurrence of Besnier-Boeck's Disease in Lung, Schweiz. med. Wchnschr. **69**:269 (March 25) 1939.

4. Boggild, D.: Probable Boeck's Sarcoid of Fingers in Sisters Two and Five Years Old: Two Cases, Nord. med. (Hospitalstid.) **21**:416 (March 3) 1944.

5. Sellei, J., and Berger, M.: Sarcoid Tumors in a Family: Sarcoid (Joseph) and Lupoid-Allergic Reaction, Arch. f. Dermat. u. Syph. **150**:47, 1926.

was diagnosed as sarcoid by the clinical courses of the patients and typical histologic pictures of tissue on biopsy. To these reports we add the records of examples of familial sarcoid.

FIRST FAMILY

CASE 1.—W. H. B., a 25 year old Negro, was first seen in the Johns Hopkins Hospital on June 13, 1946, with the chief complaint of "trouble in his chest, back and eyes." For four or five months he had had pain in the region of the kidney, which was worse on bending or stooping. There was also pain along the lower wall of the right side of the chest under the ribs, almost constantly present. For "some time" there had been redness and pain in both eyes and swelling in the parotid region (the first symptom, preceding any other by several months). He had lost 20 pounds (9 Kg.). By the time of examination the parotitis had almost completely subsided. There was some questionable dyspnea, not related to exertion. In September 1945 he noticed edema of the ankles, which gradually subsided, leaving the legs scaly. The only significant fact in the family history was that a brother had had "some sort of eye trouble." There was no history of tuberculosis. The past history and a review of the systems were essentially noncontributory.

Physical Examination.—The temperature was 100 F., the pulse rate 116 and the respiratory rate 24. The height was 66½ inches (169 cm.) and the weight 132¼ pounds (60 Kg.). The blood pressure was 110 systolic and 80 diastolic. The patient was a young Negro who had obviously lost weight and who appeared ill and somewhat pale. There was no respiratory distress. An eruption was seen on both forearms just above the wrists in the form of an annular arrangement of subcutaneous nodules, the skin over which was slightly hyperpigmented. Similar, less conspicuous nodules were present on the anterior aspect of both thighs and the left side of the scrotum. The skin over the lower part of the legs was thickened and scaly, and the hair in this region seemed brittle. There was slight tenderness over the long muscles of the back. Slight generalized glandular enlargement was noted, particularly of the posterior cervical nodes. The parotid glands were definitely enlarged. There was some injection of the conjunctivas, and the upper lids appeared swollen. The pupils were irregular in outline, due to the presence of synechias, and they reacted sluggishly to light. Medial opacities prevented accurate funduscopic examination. Hearing was poor in the right ear. The lungs were entirely clear except for questionable bronchovesicular breathing over the right infraclavicular area. The examination of the heart was noncontributory. Examination of the abdomen was made difficult by voluntary muscular tension. There was definite tenderness in the epigastrium, but no masses were felt. The remainder of the physical examination and a urinalysis showed no abnormalities.

Diagnostic possibilities considered at the time of the examination were sarcoid, tuberculosis, syphilis, brucellosis and tularemia.

Laboratory Reports.—The nonprotein nitrogen content was 38 mg. per hundred cubic centimeters, the total protein content was 6.81 Gm. and the albumin-globulin ratio was 4.50 : 2.31. The white blood cell count was 6,600 and the hematocrit reading 44.2. The corrected sedimentation rate was 1.0 mm. A serologic test of the blood for syphilis gave negative results. Agglutination tests for tularemia, gonorrhea and brucellosis gave negative results; reactions to typhoid tests were positive with O antigen in a dilution of 1 : 80 and doubtful with H antigen in a dilution of 1 : 40. Tuberculin tests with 0.001 to 0.1 mg. of old

tuberculin elicited negative reactions; a test was done with 1.0 mg., but the reaction was not read.

A roentgenologic examination of the chest showed no abnormalities of the ribs, but dense infiltrations in the region of the roots of both lungs were described as being compatible with a diagnosis of sarcoid. No evidence of sarcoid was seen in the bones of the hands, and examination of the thoracic and lumbar regions of the spine showed nothing abnormal.

One of the papules on a forearm was removed for biopsy. The histologic picture was interpreted by Dr. Lloyd Ketron as typical of sarcoid on the basis of nests of epithelioid cells in the corium, separated by connective tissue septums, the presence of giant cells and the absence of caseation.

CASE 2.—T. B., the brother of W. H. B., was a 29 year old Negro who was first seen in the Johns Hopkins Hospital on March 20, 1944, with the complaint of pain in the back. The family history and past history were noncontributory. The review of the systems was essentially noncontributory.

In August 1943 the patient had first noticed a dull, aching, nonradiating pain, with no associated symptoms, in both sides of the lower part of the back, associated with movement. In December 1943 the pain had become more constant and occurred even at rest, and swelling of the ankles and periorbital region had begun.

During January 1944, the patient noticed what he described as "visual difficulty" in the right eye. This persisted to the time of examination, along with a burning sensation in both eyes. Loud noises caused distress in the right ear. Early in February 1944 he noticed swelling of the neck and symmetric preauricular knots. In March 1944 the patient noticed aching in the left forearm, radiating to the fifth finger, generalized itching and sore throat associated with a nonproductive cough.

Physical Examination.—The temperature was 97.6 F., the pulse rate 84 and the respiratory rate 20. The weight was 138¾ pounds (63 Kg.) and the height 70½ inches (179 cm.). The blood pressure was 112 systolic and 85 diastolic. The patient was a frail young Negro. The skin was of normal texture except over the lower half of the legs, where it was scaly and roughened. The lungs were entirely clear. The examination of the heart revealed nothing unusual except for a split second sound over the precordium. There were no abnormal abdominal findings.

Both testes were unusually tender, but they were not otherwise abnormal. The finger nails were cyanotic, and the lower parts of the legs and the feet were edematous. Neurologic examination revealed paralysis of the right seventh cranial nerve of the lower motor neuron type. The remainder of the physical examination revealed nothing significant. Urinalysis revealed nothing unusual except for 2 or 3 leukocytes and 1 or 2 granular casts per high power field.

The diagnostic impression at this time was parotitis (?), unaccountable edema of the ankles and nephrosis (?).

Laboratory Reports.—The hematocrit reading was 45; the white blood cell count was 4,950; the corrected sedimentation rate was 4.0 mm. in one hour, and the icterus index was 7.5. The serologic test for syphilis gave negative results.

Roentgenologic examination of the chest showed a normal heart and aorta. There was dense clouding in each hilus and infiltration extending therefrom to involve each lung, slightly less pronounced at the bases and apexes. There was probably some enlargement of the lymph nodes at each hilus, but these were not discrete. The appearance was interpreted as being compatible with a diagnosis

of sarcoid. The roentgenogram of the hands was normal except for slight thickening of the soft tissues in the region of the proximal interphalangeal joints.

On March 28, 1944 the patient returned to the hospital with a complaint of soreness in the right eye. There was conjunctival injection and photophobia, and uveoparotid fever was considered the best possibility. He was admitted to the hospital for study. Examination on admission showed essentially the same findings as on the previous examination except for the additional presence of a dilated, fixed pupil of the right eye, blurring of the disk of the left eye, scattered crackling rales in the lower field of the left lung and indurated, enlarged and tender epididymides. The diagnostic impression then was sarcoidosis with uveitis, parotitis, Bell's palsy of the right side and bilateral epididymitis. The corrected sedimentation rate was now 16 mm. in one hour. The reaction to a tuberculin test with 0.02 mg. of purified protein derivative was negative. A biopsy of a femoral node showed only scarring and deposits of hemosiderin. The patient's three week course in the hospital was afebrile except for occasional elevations in temperature to 100 F.

After his discharge the patient was not seen again until July 27, 1944, when he returned to the hospital because of weakness of the left side of the face. The roentgenogram of his chest now showed, in addition to the previous findings, slight infiltration in the lower lobe of each lung. On Aug. 7, 1944, an ophthalmologic consultant stated that he had found bilateral granulomatous iritis which was probably due to sarcoid. On Jan. 4, 1945, roentgenologic examination of the chest showed no change. On July 20, 1945, he returned to the hospital with exacerbation of the uveitis of the left eye. Reaction to a tuberculin test at this time was negative with 0.1 mg. of old tuberculin.

SECOND FAMILY

CASE 3.—I. S., a 31 year old Negro, was first seen at Johns Hopkins Hospital on Nov. 13, 1937, having been referred for diagnosis. A complete report of this visit is not obtainable, but three nodes in the right inguinal area were excised and a biopsy specimen was taken from a finger after a clinical impression of sarcoid had been gained. The pathologic report stated that there were "hard and caseous tubercles and giant cells in the subcutaneous tissue of the finger. The clinical picture of sarcoid was present. No tubercle bacilli were found."

In September 1938 the patient was again seen, and a note was made that there were typical sarcoid lesions of the skin, especially on the arms and legs. At this examination the question of pulmonary tuberculosis was raised, as tubercle bacilli were said on one occasion to have been found in the sputum by a substitute technician. This, however, was not confirmed by subsequent examinations of the sputum.

Because of ulceration of some of the cutaneous lesions, frequency of symptoms, nocturia and hematuria, the patient was admitted to the medical service on Nov. 24, 1940.

At this time the information was obtained that he had been "sickly" since childhood, with frequent stomach aches, poor appetite and general lassitude. He had had no known contact with tuberculosis. At 18 years of age he had pneumonia with empyema, necessitating open drainage.

In 1934 he noticed swelling of the cervical lymph nodes, followed by swelling of both sides of his face. His tonsils were removed, and the swelling became more severe. At the same time he had considerable visual difficulty, with photophobia, inflammation and inability to recognize distant objects. Later, there was a definite droop of the left eyelid and his mouth became twisted to the right. The

parotitis and facial palsy gradually subsided and were succeeded by subcutaneous "lumps" in the skin, varying from pinhead sized to pea sized and nontender but itching. The swelling of the neck subsided early in 1936, but the cutaneous lesions persisted.

In March 1937, at another hospital, a roentgenogram of the fingers showed thickened soft tissues of the index finger of the left hand at the proximal interphalangeal joint. Roentgenologic examination of the chest showed an area of increased density in the lower lobe of the right lung and a large area of decreased density in the upper lobe of that lung, with possible cavitation, diffuse pleural thickening on the right, infiltration of the upper lobes of both lungs, suggestive of tuberculosis, and decided increase in the shadows of the roots. Smear cultures of the sputum failed to reveal tubercle bacilli. The corrected sedimentation rate was 40 mm. in one hour.

Physical Examination (Nov. 24, 1940).—The temperature was 99.8 F., the pulse rate 108 and the respiratory rate 24. The weight was 138 pounds (62.5 Kg.) and the height 68 inches (173 cm.). The blood pressure was 152 systolic and 110 diastolic. The patient was a well developed young Negro who appeared ill. There was a scaly dermatitis of the scalp and extremities, consisting of dry crusted nodules varying from 2 mm. to 2 cm. in diameter. Small nodules were seen in the eyelids. Motion of the right side of the chest was limited, and there was a curvature of the spine to the left. The right side of the chest was dull to percussion, and scattered rales were heard over both pulmonary fields, especially after coughing. The spleen was easily felt, and there were epitrochlear lymphadenopathy involving the right arm and a fusiform swelling of some of the fingers, especially the left index finger. The remainder of the physical examination was essentially noncontributory.

Laboratory Reports.—The blood picture was normal except that 7 per cent of the cells were eosinophils. A serologic test of the blood for syphilis gave negative results. Repeated smears and cultures of the sputum failed to reveal tubercle bacilli. The nonprotein nitrogen content of the blood was 44 mg. and the total protein content 7.6 Gm. per hundred cubic centimeters. The albumin-globulin ratio was 44:56. The basal metabolic rate was +20 per cent. The uric acid content of the blood was 5.7 mg. per hundred cubic centimeters and the cholesterol content 160 mg. In a phenolsulfonophthalein test 78 per cent of the dye was excreted in two hours. A series of gastrointestinal roentgenograms revealed a duodenal ulcer. Dr. Murray Fisher, who had been interested in the patient since 1937, was of the opinion that he had had sarcoid and that active tuberculosis had developed later. On December 23 the patient became suddenly worse, with gradually deepening coma, and he died in renal failure and alkalosis on December 27.

The pathologic diagnosis was as follows: sarcoid, with lesions in the skin, lymph nodes, lungs, pleura, liver, spleen, kidneys, testes and epididymides; scars and infiltration of mononuclear cells in the heart (healed sarcoid?); old healed tuberculosis (?) with formation of cavities in the upper lobes of both lungs; tuberculosis of the axillary lymph nodes on the right, with a sinus tract; old resection of the ribs on the right side; fibrous pleural and pericardial adhesions; history of terminal alkalosis; deposition of calcium in the renal tubules, and bilateral renal calculi.

The cavities in the lungs were surrounded by fibrous walls. No caseation was seen. The fibrous walls contained sarcoid tubercles and were surrounded with sarcoid tissue. The axillary lymph node showed typical tuberculosis in which caseation was evident and tubercle bacilli were stained. Tubercle bacilli were

found in none of the sarcoid lesions. It was the opinion of the pathologist that the cavities were not the result of sarcoid but were probably tuberculous in origin.

CASE 4.—C. S., a brother of I. S., was a 21 year old Negro, first seen in the Johns Hopkins Hospital on Dec. 21, 1938, complaining of a "sore knee joint." Ten months prior to his first visit he had lost his appetite and had noticed some shortness of breath and tachycardia. Loss of weight, which began at the same time, continued progressively up to the time of his admission to the hospital. His sputum had been examined elsewhere in April 1938, and no tubercle bacilli had been found. On November 1 his tonsils became sore and the glands under the angles of the jaw became swollen. The attacks of tonsillitis continued intermittently. A few days prior to his first visit the right knee became sore and swollen. There was no history of trauma. No other joints were involved.

Physical Examination.—The temperature was 99.8 F., the pulse rate 88 and the respiratory rate 20. The weight was 145½ pounds (66 Kg.) and the height 69½ inches (177 cm.). The blood pressure was 110 systolic and 75 diastolic. The patient was a well developed young Negro, in no obvious distress. Both tonsils were found to be mildly inflamed. The right knee was swollen, hard and tender, but there was no crepitus. The remainder of the physical examination was essentially noncontributory. Other than moderate albuminuria, urinalysis revealed nothing abnormal.

The first impression was that the patient had acute rheumatic fever, and salicylate therapy was given, without improvement. A roentgenogram of the chest showed diffuse infiltration throughout both pulmonary fields, extending from the roots of the lungs. There was definite enlargement of the hilar nodes, and the picture was interpreted by the radiologist as nontuberculous but compatible with a diagnosis of sarcoid, Hodgkin's disease or leukemia. A roentgenogram of the right knee showed fluid and pathologic changes interpreted as being due to acute infection. It was then recalled that his brother (case 3) had sarcoid, and he was admitted to the hospital for study on Dec. 28, 1938.

The only additional finding of significance at this time was that of generalized lymphadenopathy. A node in the right supraclavicular area was excised. The histopathologic picture was that of sarcoid, the lymph nodes being replaced by large tubercles, a few of which contained giant cells. The tubercles were poorly defined but were separated in some areas by narrow rows of plasma cells. In places there were small collections of lymphocytes and numerous epithelioid cells. Acid-fast stains revealed nothing unusual. Biopsy of the synovial tissue of the knee joint showed only chronic inflammation.

Laboratory Reports.—The total protein content was 6.64 Gm. per hundred cubic centimeters; the albumin-globulin ratio was 42 : 58. Reaction to a tuberculin test with 0.1 mg. of old tuberculin was negative. The electrocardiogram was normal. Agglutination tests for brucellosis and tularemia gave negative results.

On Jan. 24, 1939 an ophthalmologist found evidence of old uveitis, although the patient denied symptoms. He was not seen again until Jan. 23, 1942, when he returned with a complaint of hoarseness of five months' duration. Tubercle bacilli were found on examination of the sputum, and a roentgenogram of the chest showed extensive tuberculous infiltration, with cavities in both apexes. Since that time he has had two admissions to a sanatorium for patients with tuberculosis.

A notation in a record of the patient's history on Oct. 19, 1942 stated that "a sister, F. H., who also had sarcoid, died on Oct. 18, 1942."

CASE 5.—H. S., the brother of I. S. and C. S., was a 22 year old Negro who came to the Johns Hopkins Hospital on Jan. 28, 1939, by request, because of a history of sarcoidosis in two of his brothers. His past history was noncon-

tributory, and he had no complaints, stating that except for an occasional "chest cold" he had always enjoyed perfect health. The only thing of possible significance was that all children in the family except the patient in case 3 had come in close contact with a mule on the father's farm which "had knots all over its body." The only abnormal physical finding was inequality of the pupils, the left being larger than the right and reacting to light more sluggishly. The physical examination revealed no evidences of sarcoid. A serologic test for syphilis gave negative results. The reaction to a tuberculin test with 0.1 mg. of old tuberculin was negative. A roentgenogram of the chest revealed only a slight increase in hilar markings.

The patient next returned in January 1942, after having been rejected for the army because of "bad lungs." He complained only of pain in the chest.

Physical Examination.—The temperature was 98.2 F., the pulse rate 72 and the respiratory rate 18. The weight was 154¾ pounds (70 Kg.) and the height 69 inches (175 cm.). The blood pressure was 140 systolic and 90 diastolic. The patient was a well developed young Negro, in no obvious distress. Some small, firm, discrete cervical glands were palpable, and femoral lymphadenopathy was noted. Both epididymides were enlarged, indurated and tender. There was evidence of low grade iritis, confined to the left eye.

Laboratory Reports.—The reaction to a tuberculin test with 0.1 mg. of old tuberculin was negative, and the sputum failed to reveal tubercle bacilli on one examination. The blood picture was normal except that 7 per cent of the cells were eosinophils, and the electrocardiogram was normal. Inoculation of a guinea pig showed the urine to be negative for tuberculosis. A positive reaction to a serologic test for syphilis was interpreted as a false positive result after failure to confirm it by subsequent tests. Increased hilar shadows and a density in the middle lobe of the right lung were seen on fluoroscopy and confirmed by a roentgenogram of the chest. On biopsy an inguinal node was interpreted as "hard tubercles, probably sarcoid," on the basis of the presence of epithelioid cell nests and giant cells and the absence of caseation.

Case 6.—E. S., a brother of I. S., C. S. and H. S., was a 25 year old Negro, who first came to the Johns Hopkins Hospital on May 15, 1936, complaining of pain in the eyes and head of four weeks' duration. At the onset, vision in both eyes had become poor and cloudy and constant headaches had developed. Two abscessed teeth had been extracted, without improvement. For ten days both eyes had ached and had been "red and runny." Ophthalmologic examination revealed dull, lusterless irides, with large synechias of the right pupil. The diagnostic impression was bilateral iritis, and the patient was referred to the laryngologic clinic, where it was noted that the parotid glands were palpable and the tonsils chronically infected. The roentgenogram of the sinuses showed fluid in the right antrum. The reaction to a tuberculin test was negative with 0.1 mg. and slightly positive with 1.0 mg.

The patient was not examined in a medical clinic until Jan. 26, 1939. For two years he had had "light spots" on the lower parts of the legs.

Physical Examination.—The temperature was 97.8 F., the pulse rate 80 and the respiratory rate 18. The weight was 178¼ pounds (81 Kg.) and the height 70½ inches (179 cm.). The blood pressure was 135 systolic and 88 diastolic. The patient was a young Negro, in no obvious distress. Depigmented areas were noted on both legs. There was a cervical and axillary lymphadenopathy, impaired percussion in the right axillary region and a questionable friction rub below the right nipple. A systolic apical murmur was heard.

Laboratory Reports.—There were no abnormal contents in the urine. The reaction to a tuberculin test was positive in forty-eight hours with 1.0 mg. of old tuberculin. A roentgenogram of the chest showed linear fibrosis extending from the roots of both lungs into the perihilar regions.

COMMENT

In the first family there were 3 siblings, only 2 of whom were examined and found to have sarcoidosis. Nothing is known of the third member. There is a remarkable similarity in the symptoms and clinical course of the disease in these 2 brothers. In only 1 (case 1) did the report of the biopsy confirm the clinical impression, but there is little doubt about the diagnosis in case 2. Typical cutaneous lesions were present only in the first patient.

The second family was studied in detail so far as possible (several of the siblings lived in another state and were not available for examination). There were 10 siblings, 5 of whom were examined in the Johns Hopkins Hospital. Of the 5 who were examined, 3 (cases 3, 4 and 5) were proved to have sarcoidosis by roentgenologic examination, negative reactions to tuberculin tests at first examination and biopsy. Although the diagnosis was not proved in case 6, it is highly probable that the patient had sarcoid in view of the iritis, parotitis, only sightly positive reaction to the tuberculin test with 1.0 mg. of old tuberculin and subsequent appearances in the roentgenograms. One other patient who was examined at the Johns Hopkins Hospital is not reported on in detail because of lack of sufficient evidence for a definite diagnosis. However, sarcoid is suspected in this patient also.

There is a notation in the record of the history of the patient in case 4 which states that a sixth sibling had died after a diagnosis of sarcoid had been made elsewhere. No confirmation of this statement is available.

In only 1 member of this family (case 3) were definite cutaneous lesions described by the examining physicians.

Active tuberculosis ultimately developed in the patients in cases 3 and 4, but in each instance three years had elapsed since the original diagnosis of sarcoid had been established by repeated negative results of examinations of sputum, negative reactions to tuberculin tests, uveoparotitis and biopsy.

SUMMARY

Sarcoidosis occurred in siblings of two unrelated families. In one family at least 2 of the 3 siblings were affected, and in the other a diagnosis was established for 3 siblings and was probable or possible for at least 3 others of a total of 10 siblings. Cutaneous lesions were found in only 2 of the patients discussed. Active tuberculosis ultimately developed in 2 patients.

Dr. Murray Fisher of the Department of Medicine, Johns Hopkins Hospital, allowed us to use the material which he had accumulated regarding family 2.

HEPATITIS WITHOUT JAUNDICE IN INFECTIOUS MONONUCLEOSIS

QUIN B. DeMARSH, M.D.
AND
HOWARD L. ALT, M.D.
CHICAGO

JAUNDICE was first recognized as a complication of infectious mononucleosis by Mackey and Wakefield in 1926.[1] A single case in which a patient with this disease exhibited jaundice had been noted previously by Downey and McKinlay.[2] The incidence of jaundice in different reported series of cases of infectious mononucleosis has varied from 1.3 to 12.8 per cent.[3] At first, it was postulated that jaundice was due to blocking of the common duct by enlarged lymph glands.[4] Later evidence acquired by tests of hepatic function [5] and by biopsies of material obtained with the punch [6] indicates that jaundice is secondary to parenchymatous changes in the liver. From a single biopsy of the liver, Kilham and Steigman [6a] described a well defined focal acute hepatitis. They said: "the maximum change is seen in the portal tracts of the lobules where there is loss of liver cells and a well developed histiocytic reaction with some early proliferation of bile ducts."

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From the Department of Medicine, Northwestern University Medical School. School.

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The histologic changes in 4 cases described by Bang and his co-workers[6b] consist of periportal infiltration, cloudy swelling, vacuolation of hepatic cells and some areas of focal necrosis. It was their impression that the pathologic changes were similar to those seen in infectious hepatitis.

Little attention has been drawn to the hepatic function in non-jaundiced patients with infectious mononucleosis. Mention frequently has been made of enlargement of the liver in this disease (12 per cent in Bernstein's series [7]), but tenderness seldom has been noted. In 1944 Ziegler [8] reported the observations made at autopsy in a case of infectious mononucleosis in a young woman who died of a ruptured spleen. Before death, the liver was palpable and tender but there was no jaundice. The microscopic changes noted were similar to those described [6a, b] as seen in jaundiced patients.

Recently, Cohn and Lidman [9] reported serial tests of hepatic function in 15 consecutive cases of infectious mononucleosis, in none of which was there jaundice. Every patient had definite evidence of impaired hepatic function that persisted for periods of three to eight weeks. One patient, not included in the series, had a persistence of hepatic damage and was considered to have chronic hepatitis on the basis of infectious mononucleosis. The authors felt that diet, vitamin therapy and rest shortened the course of the disease.

At the time that the aforementioned article appeared we had begun a similar study. In the present report it is further shown that hepatic involvement occurs in the great majority of cases of infectious mononucleosis.

MATERIAL AND METHODS

Serial tests of hepatic function were performed in 19 consecutive cases of infectious mononucleosis observed by us between January and August 1946. None of the patients had jaundice. The subjects consisted of 16 students from the professional schools at Northwestern University, 2 private patients and 1 clinic patient. The diagnosis of the disease was based on the usual criteria, namely, the clinical picture, the presence of atypical lymphocytes in the blood and a positive reaction to the heterophile antibody test in serum dilutions of 1 to 160 or over. Since many more cases were encountered in students during the first half of 1946 than in the same period in previous years a mild epidemic was considered to have occurred. A number of students were thought to have an extremely mild form of the disease, but since evidence in favor of a diagnosis of infectious mononucleosis was equivocal they were not included in this study. It was not always possible to make tests of hepatic function as often or for as long a period as was desired, since many of the students went home soon after the diagnosis was made or left school for summer vacations.

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Heterophile antibody tests were performed by the original technic of Davidsohn [10] and recorded according to actual serum dilution.[7] Agglutination in a dilution of 1 to 160 or over was considered as a positive reaction. Tests of hepatic function performed routinely were the icterus index test, the cephalin-cholesterol flocculation test [11] and the sulfobromophthalein excretion test. Normal values for the icterus index range from 4 to 7 units.[12] For the cephalin-cholesterol flocculation test, values of 2 plus or over in forty-eight hours or less were considered abnormal.[13] In the performance of the sulfobromophthalein test, 5 mg. of the dye per kilogram of body weight was injected and blood was drawn either in forty-five minutes or in thirty and sixty minutes. Retention of dye up to 10 per cent in thirty minutes [14] and complete excretion in forty-five minutes and sixty minutes [15] were considered normal. Determinations of serum albumin and globulin contents were made in 9 cases.

RESULTS

Some degree of hepatic dysfunction as shown by the cephalin-cholesterol flocculation and/or the sulfobromophthalein excretion test was present in all 19 cases of infectious mononucleosis (table). The icterus index was normal in 13 cases, and in 5 it ranged from 8 to 10 units. These values may represent slight hyperbilirubinemia, but no clinical jaundice was present. The reaction to the cephalin-cholesterol flocculation test was positive in 15 of 18 cases in which the test was performed. Of the 3 cases in which the reaction was negative, in 2 (cases 1 and 4) the disease was in a late stage and in 1 (case 15) there was an extremely mild form of the disease. Hepatic damage in these 3 patients was indicated by the retention of sulfobromophthalein. In most cases the reaction to the cephalin-cholesterol flocculation test was still positive after the excretion of sulfobromophthalein had returned to normal. The sulfobromophthalein test showed an abnormal retention in 15 of the 19 cases. The maximum retention was 36 per cent (case 8) in forty-five minutes. All the 4 patients having no retention of dye had a positive reaction to the cephalin-cholesterol flocculation test. An abnormal albumin-globulin ratio was present in 2 (cases 1 and 16) of 9 cases.

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Case; Sex; Age	Date (Approximate Onset of Symptoms in Parenthesis)	Heterophile Agglutination, Dilution	Icterus Index, Units	Cephalin-Cholesterol Flocculation		Retention of Sulfobromophthalein, per Cent			Serum Albumin, Gm. per 100 Cc.	Serum Globulin, Gm. per 100 Cc.	Liver *	Spleen *	Symptoms
				24 Hr.	48 Hr.	30 Min.	45 Min.	60 Min.					
1	(12/25/45)												
M	1/16/46	.....	8	..	..	..	6	..	3.7	3.4	0 T	P	Mild
20 yr.	1/24/46	1:320	8										
	4/16/46	.....	..	..	..	..	12	..	5.1	3.1	P 0	P	
	5/24/46	.....	..	..	..	..	..	..	...	...	P 0	P	
	6/12/46	1:10	7	0	0	4	..	0					
2	(2/25/46)												
M	2/25/46	1:2,560											
20 yr.	3/ 8/46	.....	10	++++	..	..	21	..	5.0	2.8	P T	P	Mild
	3/11/46	.....	8	..	..	..	4	..	4.6	2.6	P T	P	
	3/19/46	.....	6	++++	..	..	..	..	...	...	P T	P	
	3/25/46	1:2,560	..	..	..	..	..	..	...	...	P T	P	
	4/ 3/46	.....	10	..	..	..	2	..	...	...	P T	P	
	4/16/46	1:1,280	9	++++	..	4	..	0	...	...	P 0	0	
	5/28/46	.....	..	+++	+++	..	..	..	...	...	P 0	0	
	6/18/46	.....	..	0	0	..	..	..	...	...	P 0	0	
3	(2/24/46)												
M	3/15/46	.....	..	..	..	..	..	..	...	...	0 0	P	Severe
22 yr.	3/19/46	1:320	5	++++	..	..	12	..	4.2	2.8	0 0	P	
	3/22/46	.....	..	++++	..	..	..	..	...	...	0 0	0	
	3/26/46	.....	..	++++	..	..	8	..	...	...	0 0	0	
	5/ 6/46	1:320	..	++	++++	..	6	..	...	...	0 0	0	
	5/23/46	.....	..	+++	+++	..	..	..	...	...	0 0	0	
	6/24/46	.....	..	0	+	..	..	..	...	...	0 0	0	
4	(3/ 1/46)												
M	3/21/46	.....	..	..	..	..	..	..	...	...	P 0	P	Mild
6 yr.	4/ 2/46	1:2,560											
	4/16/46	.....	5	+	+	8	..	4	...	...	P 0	P	
	4/30/46	.....	..	0	0	4	..	0	...	...	0 0	0	
5	(3/29/46)												
M	4/ 2/46	1:2,560	6	++++		..	4	..	...	...	0 0	P	Mild
22 yr.	4/12/46	1:2,560	..	+++	++++	0	..	..	...	...	0 0	0	
6	(4/ 4/46)												
M	4/ 4/46	1:160	..	0	+	..	..	..	...	...	0 0	P	Mild
23 yr.	4/ 9/46	.....	..	..	..	16	..	4	...	...	0 0	P	
	4/16/46	1:40	7	..	..	..	11	7	...	...	P T	P	
	4/23/46	.....	..	..	..	..	14	10	4.6	2.6	P T	P	
	4/29/46	.....	..	++++	..	8	..	4	...	...	P T	P	
	5/10/46	1:2,560	..	++++	..	12	..	4	...	...	0 0	P	
	6/ 4/46	.....	..	+	+++	12	..	6	5.3	2.9	0 0	P	
7	(4/ 5/46)												
M	4/10/46	1:2,560	..	+	++	5	..	0	...	...	0 0	P	Mild
27 yr.	4/17/46	.....	6	+	++	4	..	0	...	...	0 0	P	
	4/24/46	.....	..	0	0	..	..	..	...	...	0 0	0	
8	(4/23/46)												
M													

* P indicates palpable and T tender; 0 in the columns headed "Liver" and "Spleen" indicates not palpable or not tender.

* P indicates palpable and T tender; 0 in the columns headed "Liver" and "Spleen" indicates not palpable or not tender.

8	(4/23/46)													
M	4/24/46	1:80	..	..	..	..	..	..	....	....	0	0	0	Mild
24 yr.	5/11/46	1:320	7	+++	++++	8	..	0	....	....	0	0	0	
	5/27/46	.....	..	+	+++	..	..	..	....	....	0	0	0	
9	(4/26/46)													
M	5/ 1/46	1:1,280	..	0	+	0	..	..	....	....	0	0	P	Mild
25 yr.	5/14/46	.....	6	+	+++	0	..	..	....	....	P	T	P	
	6/17/46	.....	..	0	0	..	..	..	....	....	0	0	0	
10	(4/27/46)													
M	5/10/46	1:2,500	..	++++	..	30	..	15	....	....	P	T	0	Severe
22 yr.	5/17/46	.....	6	++++	..	25	..	4	....	....	0	0	0	
	5/24/46	.....	..	0	++	4	..	0	....	....	0	0	0	
	7/20/46	.....	..	0	+									
11	(5/ 6/46)													
M	5/10/46	1:1,280	9	++++	..	..	12	..	....	....	0	0	P	Severe
21 yr.	5/22/46	.....	5	++++	..	..	0	..	5.0	3.2	0	0	0	
12	(5/22/46)													
M	6/ 1/46	1:320	6	+++	++++	..	20	..	4.6	1.7	0	0	0	Severe
22 yr.	6/ 7/46	1:2,560												
	6/10/46	.....	6	+++	+++	..	8	..	....	....	0	0	0	
13	(6/ 6/46)													
M	6/ 7/46	.....	..	..	..	..	..	..	....	....	0	0	P	Severe
21 yr.	6/10/46	1:640	..	..	..	..	12	..	4.1	1.8	0	0	P	
	6/22/46	.....	..	..	..	..	0							
14	(6/ 6/46)													
M	6/10/46	1:2,500	..	..	..	..	..	..	....	....	0	0	0	Mild
21 yr.	6/17/46	.....	5	+++	++++	4	..	0	4.4	2.7	0	0	0	
	6/24/46	.....	..	++	+++	0	..	..	....	....	0	0	0	
	7/27/46	.....	..	0	0									
15	(6/ 6/46)													
M	6/ 8/46	1:80	..	..	..	..	..	..	....	....	0	0	0	Mild
21 yr.	6/11/46	.....	7	0	0	8	..	4	....	....	P	T	P	
	6/17/46	1:160	..	0	0	0	..	..	....	....	0	0	0	
16	(6/10/46)													
F	6/17/46	1:640	..	..	..	..	..	..	....	....	0	0	0	Severe
28 yr.	6/20/46	1:1,280	8	+++	++++	..	..	36	3.4	3.0	0	T	0	
	6/27/46	.....	8	..	..	..	..	30	3.4	2.3	0	0	0	
	7/17/46	.....	6	..	..	0	..	..	4.6	3.6				
17	(6/12/46)													
M	6/17/46	1:160	7	0	+	20	..	8	....	....	0	0	0	Severe
24 yr.	7/ 1/46	.....	..	+++	++++	5	..	0	....	....	0	0	0	
18	(7/ 2/46)													
M	7/12/46	1:160	..	..	..	30	..	8	....	....	0	0	0	Severe
21 yr.	7/13/46	.....	8	++++	..	..	36	..	....	....	0	0	0	
	7/22/46	.....	..	..	..	..	24	..	....	....	0	0	0	
	7/24/46	1:1,280	..	++++	..	..	..	..	....	....	0	0	0	
	7/26/46	.....	..	..	..	..	16	..	....	....	0	0	0	
19	(7/29/46)													
M	8/ 3/46	1:160	5	0	0	..	6	..	....	....	0	0	0	Moderate
23 yr.	8/ 5/46	.....	..	..	..	..	..	..	....	....	0	0	P	
	8/19/46	1:7,188	..	+++	++++	..	2	..	....	....	0	0	0	
	8/26/46	.....	..	0	0	..	0	..	....	....	0	0	0	

Reactions to the initial tests of hepatic function, made from one to twenty-four days after the onset of symptoms, were positive in 17 patients. Thereafter the degree of hepatic dysfunction regressed, and 12 cases were followed until the tests yielded normal results. There seemed to be some correlation between the severity of symptoms and the degree of hepatic damage. Five patients (cases 10, 11, 12, 16 and 18) who had high fever and prostration for five to seven days all had rather high retention of dye. In 7 patients (cases 5, 7, 8, 9, 14, 15 and 19), who had a mild type of infectious mononucleosis with only slight or no fever and malaise, hepatic dysfunction was minimal. The presence of hepatic involvement might be questioned in cases 7 and 9, but it is indicated by the return to normal of the cephalin-cholesterol flocculation from a 2 plus and 3 plus reaction.

The average duration of disease of the liver, as shown by tests of hepatic function, was from two to six weeks. An unusually long period of hepatic involvement occurred in cases 1, 2 and 3, in which the reactions to test of hepatic function remained positive for four and one half, three and two months respectively. The first 2 patients had mild attacks of infectious mononucleosis, while the third patient was decidedly ill and had fever for about three weeks. These and other patients in the series felt comparatively well before the reactions to the tests of hepatic function became negative.

The occurrence and duration of enlargement and tenderness of the liver and of splenomegaly are shown in the table. The liver was palpable in 7 cases and continued to be so for varying periods. Tenderness over the region of the liver occurred at some time in 7 patients; in 2 of these the liver was not palpable at the time when it was tender. Tenderness was usually transient, but it persisted for two weeks in case 6 and for four weeks in case 2. The spleen was palpable in 12 cases (63 per cent). Three patients (cases 1, 2 and 6) who had a persistence of splenomegaly for one to four months also had a prolonged period of hepatic involvement.

All the patients in this series were given rest in bed until their temperature returned to normal. In addition, they were given a high protein, high carbohydrate diet, dried yeast powder and multivitamin preparations. We have no evidence that the course of the disease was altered by the dietary regimen or by the vitamin supplements. Most of the patients resumed moderate activity, such as going to classes, before the hepatic function had returned to normal. There was no correlation in this group between subjective symptoms and the persistence of hepatic damage; some felt well, while others had malaise and easy fatigability. None of the patients had a relapse of hepatic disease as indicated by tests of hepatic function or by an increase in the size of the liver.

COMMENT

According to the report of Cohn and Lidman[9] and from our own results, it is apparent that impaired hepatic function occurs in practically all cases of infectious mononucleosis. The degree of hepatic damage is seldom sufficient to cause jaundice. The few histologic descriptions of the liver reported in cases of both jaundiced and nonjaundiced patients with mononucleosis uncomplicated by sepsis have revealed the presence of hepatitis.[16] It might then be assumed that hepatitis is almost invariably a pathologic characteristic of infectious mononucleosis.

Involvement of the liver occurs early in infectious mononucleosis, along with changes in the lymph glands and spleen. As enlargement and/or tenderness of the liver were present in 8 of our 19 cases, these signs are considered to be of diagnostic significance. The degree and duration of hepatic damage can be obtained from serial determinations of the cephalin-cholesterol flocculation and from sulfobromophthalein excretion tests. Hepatic insufficiency may subside in a few weeks, or it may persist for months.

Infectious mononucleosis with hepatitis must be differentiated from mild infectious hepatitis without jaundice. In the latter disease there may be adenopathy, splenomegaly and atypical lymphocytes in the blood.[17] The distinguishing feature in infectious mononucleosis is the presence of heterophil agglutinins in high titers; also, the adenopathy, splenomegaly and blood picture are usually more distinctive than in infectious hepatitis.

Because of the possibility of permanent hepatic damage or exacerbations of hepatic dysfunction, the state of the liver should be considered in the management of infectious mononucleosis. Lessons recently learned about the treatment of infectious hepatitis might well be applied to infectious mononucleosis. Probably the most important principle of treatment is rest in bed or decided restriction of activity until hepatic function returns to normal. It is questionable whether an increased intake of protein and carbohydrate alters the course of involvement of the liver in a young person with infectious mononucleosis who has been taking an optimal diet. However, until more evidence is available, such a diet, with vitamin supplements, is advisable. Drugs known to have a toxic effect on the liver (arsenicals, sulfonamide compounds and others) and alcohol are certainly to be avoided. The possible after-effects of this type of hepatitis, such as increased vulnerability of the liver to malnutrition and intoxication, cannot be excluded.

16. Kilham and Steigman.[6a] Bang and Wanscher.[6b] Ziegler.[8]

17. Barker, M. H.; Capps, R. B., and Allen, F. W.: Acute Infectious Hepatitis in the Mediterranean Theater, J. A. M. A. **128**:996 (Aug. 4) 1945. Hoagland, C. A., and Shank, R. E.: Infectious Hepatitis: A Review of Two Hundred Cases, ibid. **130**:615 (March 9) 1946.

SUMMARY

In 19 consecutive cases of infectious mononucleosis without jaundice varying degrees of hepatic dysfunction were present. This was shown by serial cephalin-cholesterol flocculation and sulfobromophthalein excretion tests. The duration of hepatic involvement ranged from two weeks to five months. Enlargement and tenderness of the liver were common physical findings.

303 East Chicago Avenue.

AORTIC STENOSIS WITH ELEVATED METABOLIC RATE SIMULATING HYPERTHYROIDISM

JASPER A. SMITH, M.D.
WATERBURY, CONN.
AND
SAMUEL A. LEVINE, M.D.
BOSTON

ONE OF the most gratifying experiences in the care of patients suffering from cardiovascular disease is the treatment of patients with thyrocardiac disease. This is true whether the cardiac disability is entirely due to thyrotoxicosis or whether there is an additional independent cardiac lesion. Such patients respond so well to proper management and often have so few of the customary signs of thyrotoxicosis that physicians have been impelled to search carefully for these cases of masked thyrotoxicosis. The result is that on minor suspicion determinations of basal metabolism are frequently performed in order not to overlook thyrotoxicosis as a remediable burden in patients suffering from various types of cardiac disability. At times the decision is difficult, because there are numerous other causes of an elevated basal metabolism apart from hyperthyroidism. Peabody and Wentworth [1] pointed out that cardiac failure itself caused an increase in consumption of oxygen and estimated that if the vital capacity fell below approximately 60 per cent of normal further degrees of failure would cause an increase in metabolism roughly proportional to the degree of failure. Hamburger and Lev,[2] Shapiro [3] and Resnick and Friedman [4] confirmed these observations, and it was suggested that the cause of the increased basal metabolic rate in cardiac failure was largely the muscular effort

From the Medical Clinic of the Peter Bent Brigham Hospital and the Department of Medicine, Harvard Medical School, Boston.

1. Peabody, F. W.; Wentworth, J. A., and Barker, B.: Clinical Studies on the Respiration: The Basal Metabolism and the Minute-Volume of the Respiration of Patients with Cardiac Disease, Arch. Int. Med. **20**:468 (Sept.) 1917.

2. Hamburger, W. W., and Lev, M. W.: Basal Metabolism in Organic Heart Disease with Congestive Failure, J. A. M. A. **84**:587 (Feb. 21) 1925.

3. Shapiro, S.: The Basal Metabolic Rate in Cases of Chronic Cardiac Disease and in Cases of Hypertension, Arch. Int. Med. **38**:385 (Sept.) 1926.

4. Resnick, H., Jr., and Friedman, B.: Studies on the Mechanism of the Increased Oxygen Consumption in Patients with Cardiac Disease, J. Clin. Investigation **14**:551 (Sept.) 1935.

involved in dyspnea. Riesman [5] called attention to the fact that hypertension of itself was capable of simulating hyperthyroidism in some instances, and Boas and Shapiro [6] substantiated this clinical observation with determinations of basal metabolic rate in a series of hypertensive patients, stating that this syndrome most frequently occurred in those having appreciable elevation of both systolic and diastolic levels. There are additional conditions in which the metabolism may be somewhat elevated, such as polycythemia,[7] leukemia,[8] pregnancy,[9] coarction of the aorta [10] and cardiac failure associated with beriberi.[11] Apart from these, fever, severe anemia and emotional excitement can produce an elevation in the metabolic rate, and no doubt there are still other disorders in which the metabolism is elevated.

We have been confronted with a group of patients with aortic stenosis and well marked elevations in metabolic rate in whom the degree of cardiac failure was too slight to account for these elevations. The patients also showed clinical features resembling thyrotoxicosis and yet had normal thyroid glands. The purpose of this communication is to report 4 authenticated cases of such a syndrome.

REPORT OF CASES

CASE 1.—A woman entered the hospital on Nov. 29, 1933, complaining of choking cough, weakness and dyspnea of ten months' duration. She had had attacks of rheumatic fever in childhood and early adult life. She had lost 15 pounds (6.8 Kg.) during the previous year. Ten months before her admission to the hospital she contracted a severe respiratory infection, with a productive cough. This was followed by increasing dyspnea, weakness and spasmodic attacks of coughing. Three months before her admission she coughed up a cupful of bright blood and had to quit her work. Her appetite was poor, and she steadily grew worse.

Examination showed a slightly cyanotic, moist skin. There was slight lid-lag but no exophthalmos. The thyroid was palpable and was regarded as slightly enlarged. The chest was hyperresonant; expiration was prolonged, and a few

5. Riesman, D.: Hypertension in Women, J. A. M. A. **73**:330 (May 2) 1919.

6. Boas, E. P., and Shapiro, S.: Diastolic Hypertension with Increased Basal Metabolism, J. A. M. A. **84**:1558 (May 23) 1925.

7. Minot, G. R., and Buckman, T. E.: Erythremia (Polycythemia Rubra Vera): The Development of Anemia; the Relation to Leukemia; Consideration of the Basal Metabolism, Blood Formation and Destruction and Fragility of the Red Cells, Am. J. M. Sc. **166**:469 (Oct.) 1923.

8. Gunderson, A. H.: The Basal Metabolism in Myelogenous Leukemia and Its Relation to the Blood Findings, Boston M. & S. J. **185**:785 (Dec. 26) 1921.

9. Root, H. F., and Root, H. K.: The Basal Metabolism During Pregnancy and the Puerperium, Arch. Int. Med. **32**:411 (Sept.) 1923. Sanderford, I., and Wheeler, T.: The Basal Metabolism Before, During and After Pregnancy, J. Biol. Chem. **62**:329 (Dec.) 1924.

10. Blackford, L. M.: Coarctation of the Aorta, Arch. Int. Med. **41**:702 (May) 1928.

11. Okada, S.; Sakurai, E.; Ibuki, T., and Kabeshima, H.: Basal Metabolism in Vitamin B Starvation, Arch. Int. Med. **40**:292 (Sept.) 1927.

crackling rales were heard at the bases. The heart was enlarged, the rhythm was regular and a palpable systolic thrill was felt at the base. A loud systolic and a blowing diastolic murmur were heard at the base. At the apex the diastolic murmur had a rumbling quality. The blood pressure was 130 systolic and 80 diastolic; the liver was not enlarged, and there was no pitting edema. There was no tremor of the fingers. The Hinton test of the blood gave a negative reaction, and repeated examinations of the sputum showed no tubercle bacilli. The electrocardiogram showed left axis deviation. Roentgenologic examination showed pulmonary congestion, enlargement of the left ventricle and left auricle and calcification of both the aortic and the mitral valves.

The clinical diagnosis was rheumatic aortic and mitral stenosis with congestive heart failure. The patient responded favorably to digitalis and diuretic therapy. On the fourteenth and seventeenth days of her stay, when she was comfortable and much improved, the basal metabolic rate was found to be + 35 and + 37 per cent respectively.

The question of thyrotoxicosis was debated but remained in doubt. It was decided that an operation should be performed, in the belief that even if the gland proved to be normal some help might be obtained. However, after transfer of the patient to the surgical service fever developed, and she had a rapidly downhill course and died without an operation being performed.

Postmortem examination revealed chronic rheumatic heart disease, with aortic and mitral stenosis, bronchopneumonia and pulmonary thrombosis. The weight of the heart was 580 Gm. The thyroid gland was normal both grossly and microscopically.

Comment.—The loss of 15 pounds (6.8 Kg.) in weight and the slight exophthalmos, palpable thyroid, moist skin and elevated metabolic rate, at a time when the patient was not dyspneic and showed little congestion, all suggested thyrotoxicosis, but the thyroid gland was normal.

CASE 2.—A 51 year old painter entered the hospital on May 7, 1934, complaining of increasing breathlessness, especially at night. He had a history of an old peptic ulcer, and roentgenologic examination had previously shown an active duodenal ulcer. There was no history of rheumatic fever. About two years before his admission to the hospital he had definite anginal pain on walking and slight breathlessness. Later, typical attacks of paroxysmal nocturnal dyspnea developed. Some years ago he had weighed 202 pounds (98 Kg.), and this weight had steadily fallen to 150 pounds (68 Kg.), though until recently he had had a voracious appetite.

The skin was moist. There was no exophthalmos, and the thyroid was not enlarged. The heart was considerably enlarged; the rhythm was regular, and there were a loud, harsh aortic systolic murmur and a faint diastolic blow. A definite systolic thrill was felt at the base. At the apex both a loud systolic and a faint mid-diastolic murmur were heard. The blood pressure was 114 systolic and 54 diastolic. Moist rales were heard at the bases of the lungs, and the liver was definitely enlarged. There was no pitting of the ankles.

The electrocardiogram revealed left bundle branch block; the Hinton test gave a negative reaction, and the blood cholesterol content was 186 mg. per hundred cubic centimeters. A roentgenogram of the chest on the patient's twenty-first day in the hospital showed calcification of the aortic valve and calcification of a coronary artery. At that time there was no pulmonary congestion. Four determinations of basal metabolism were made, on the tenth, eleventh, thirteenth and seventeenth days of his stay, and the rates were + 48, + 53, + 34 and + 38 per cent respectively. These were all taken when dyspnea and pulmonary congestion were absent. The vital capacity during these days was around 2,500 cc.

The patient's clinical condition improved considerably on administration of digitalis and mercurial diuretics. The diagnosis was calcific aortic stenosis, with slight insufficiency, angina pectoris and coronary sclerosis. Because of the possibility of thyrotoxicosis, administration of 10 drops of strong solution of iodine U.S.P. three times daily was started on the fourteenth day of his stay and continued thereafter. The basal metabolic rate appeared to fall somewhat with the patient on iodine therapy. He was transferred to the surgical service, though it was not certain whether he had thyrotoxicosis. It was planned at that time to perform a total thyroidectomy. The day before the scheduled operation, while sitting in bed, he reached for a glass of water and died instantly.

Postmortem examination showed an enlarged heart, weighing 640 Gm. The aortic valve was strikingly calcified and stenosed, and there were multiple old small healed myocardial infarctions, calcified coronary arteries and a healed duodenal ulcer. The thyroid gland was grossly and microscopically normal.

Comment.—This patient with calcific stenosis and angina pectoris had several features suggestive of thyrotoxicosis. There was much loss of weight, with a good appetite, and a decided elevation of the basal metabolic rate, which persisted when he was well compensated and which fell definitely when he was on iodine therapy. Despite this, the thyroid gland was normal.

Case 3.—A woman 69 years old first entered the hospital on May 31, 1933. She had had rheumatic fever at the age of 19 and diabetes since the age of 60. In 1929 she had a nervous breakdown and was sick for several months. The usual weight was 148 pounds (67 Kg.), but within about a year it had fallen to 108 pounds (49 Kg.). A year before her admission to the hospital she first had sudden dyspnea while carrying some packages and had been short of breath on slight effort ever since.

Examination showed that the skin was moist, the eyes were not prominent and the thyroid was not palpable. The heart was somewhat enlarged, the rhythm was regular and a grade 4 systolic murmur was heard in the aortic area and less well heard over the precordium. No diastolic murmurs could be heard anywhere. The apical first sound was accentuated. The blood pressure was 160 systolic and 90 diastolic. The lungs showed scattered coarse rales; the liver was not palpable, and there was no peripheral pitting. There was a slight tremor of the fingers.

Laboratory examination showed a blood sugar content of around 200 mg. and a blood urea nitrogen level of 8 mg. per hundred cubic centimeters. An electrocardiogram showed left axis deviation with normal sinus rhythm. A roentgenogram of the chest showed cardiac enlargement, with a calcified mass in the region of the aortic valve and slight pulmonary congestion. The urine contained an occasional trace of albumin and sugar. The basal metabolic rate was + 31, + 46 and + 29 per cent on the second, third and ninth days in the hospital.

Clinically, the patient improved on digitalis and insulin therapy. Because of the possibility of thyrotoxicosis in addition to rheumatic heart disease, administration of strong solution of iodine was started on the fourth day, and ten days later a subtotal thyroidectomy was performed, with procaine hydrochloride anesthesia. About nine tenths of the gland was removed. The patient left the hospital improved. Pathologic examination of the specimen of thyroid removed revealed a normal gland. Her subsequent course was not satisfactory. In October 1933 the basal metabolism on two occasions was + 19 and + 22 per cent, despite the previous removal of nine tenths of the thyroid gland. Later, congestive failure became more prominent and refractory to therapy, and the patient died on Jan. 25, 1935.

Postmortem examination showed calcified rheumatic stenosis of the mitral and aortic valves. The weight of the heart was 420 Gm. The lungs showed broncho-

pneumonia and pulmonary infarction. The residual thyroid tissue was normal grossly and microscopically.

Comment.—This patient with rheumatic aortic and mitral stenosis had a definitely elevated basal metabolic rate at a time when there was little objective evidence of congestion and practically no dyspnea. A slight elevation in basal metabolic rate persisted even after removal of nine tenths of the gland. Both the surgical specimen and the autopsy material showed normal thyroid tissue.

CASE 4.—A 57 year old woman entered the hospital on Feb. 20, 1944, complaining of shortness of breath of two and a half years' duration and increasing weakness. There was no history of rheumatic fever. Her present illness was precipitated when she ran for a streetcar, at which time she became breathless and then fainted, and she had been invalided ever since, remaining in bed a good deal of the time. Dyspnea progressed, and she noticed pain in the chest radiating down both arms on effort.

Examination showed the skin to be warm and moist. There was no exophthalmos or lid-lag; the thyroid was not enlarged. There was slight tremor of the fingers. The heart was somewhat enlarged; the rhythm was regular, and there was a grade 3 aortic systolic murmur. No diastolic murmurs were heard. No thrills were felt. There was alternation of the radial pulse and also of the intensity of the systolic murmur. The blood pressure was 110 systolic and 90 diastolic. The lungs showed rales and a slight amount of fluid at the bases. The liver was possibly somewhat enlarged, and there was no pitting edema.

Roentgenologic study revealed an old tuberculous lesion of the upper lobe of the right lung, considerable pulmonary congestion, slight hydrothorax on the left side and a calcified mass in the region of the aortic valve. One week later a roentgenogram showed disappearance of the pulmonary congestion and the pleural fluid. The blood urea nitrogen content was 15 mg. and the blood cholesterol level was 298 mg. per hundred cubic centimeters. The electrocardiogram showed intraventricular block, with a normal sinus rhythm. The basal metabolic rate was + 38, + 39, + 41 and + 42 per cent on the ninth, sixteenth, eighteenth and twentieth days in the hospital respectively.

The patient improved satisfactorily on administration of digitalis, mercury diuretics and a salt-free diet. Therapy with strong solution of iodine was started on the thirteenth day and continued thereafter. She showed no obvious evidence of cardiac failure after the sixth day of her stay in the hospital. On the twenty-third day a subtotal thyroidectomy was performed, with the removal of seven eighths of the gland. Just as the operation was finished she went into collapse, the blood pressure fell and she died suddenly. Histologic examination of the gland revealed it to be entirely normal, five different sections having been examined. Permission for autopsy was not obtained.

Comment.—This patient had undoubted aortic stenosis, as evidenced by the physical findings and the detection of aortic valvular calcification by fluoroscopy. She had a persistent elevation of the basal metabolic rate, in the region of + 40 per cent, at a time when pulmonary congestion and dyspnea were insignificant. This was not influenced by iodine therapy. Though permission for postmortem examination was not obtained, most of the thyroid gland was removed at operation and found to be normal.

The 4 patients in this report had calcific aortic stenosis, and 2 also had mitral stenosis. The main point of interest is that they all showed decided elevation of the basal metabolic rate on repeated examination at times when there was little if any dyspnea or pulmonary congestion.

Despite this, the thyroid gland was grossly and microscopically normal in all cases. Each case presented some of the other clinical features suggestive of thyrotoxicosis, such as pronounced loss of weight, moist skin, slight tremor of the fingers, slight enlargement of the thyroid and exophthalmos. In none did a striking decrease in metabolism on administration of strong solution of iodine occur, though a slight fall was observed. It is of interest that in all 4 instances the heart beat was regular though congestive failure had been present, when ordinarily auricular fibrillation with cardiac failure is expected in thyrotoxicosis. It must be emphasized that these patients displayed as much apparent clinical evidence of thyrotoxicosis as many others we have seen who were proved to have a toxic thyroid gland.

The cause of the elevated metabolic rate in these patients remains obscure. It has been suggested that the increased weight of the heart (500 Gm.) of itself can increase the basal metabolic rate to as high as + 20 per cent even in the absence of congestive failure, because of increased consumption of oxygen of the cardiac muscle.[4] This explanation does not appear to be satisfactory, as an analysis of 7 other random cases of aortic stenosis coming to autopsy failed to confirm this observation. The average weight of the heart in this group was 533 Gm., and the average basal metabolic rate was + 3 per cent. The readings in metabolism, in fact, ranged from a low of — 4 to a high of + 12 per cent. To be sure, some of these patients may normally have had the low metabolic rate of hypothyroidism, and a slight increase may have developed as a result of cardiac hypertrophy.

The inference from this study is that there are some patients with aortic stenosis, with or without mitral stenosis, who have a persistent elevation of the basal metabolic rate even when dyspnea and pulmonary congestion are inconspicuous or absent, and who may also show other clinical evidence suggesting hyperthyroidism, but have a normal thyroid gland. It is suggested that determination of protein-bound iodine as a measure of thyroid function may prove helpful in a differential diagnosis. Such determinations were not made in this study.

CONCLUSION

Four cases of aortic stenosis without significant pulmonary congestion or dyspnea are reported in which the patients showed definite and persistently elevated basal metabolic rates and had normal thyroid glands grossly and microscopically. They also manifested some of the other features suggestive of thyrotoxicosis. This adds another group of conditions that needs to be considered in the differential diagnosis of masked thyrocardiac disease.

77 Central Avenue (Dr. Jasper A. Smith).
270 Commonwealth Avenue (Dr. Samuel A. Levine).

TREATMENT OF ALLERGY TO INSULIN WITH DIPHENHYDRAMINE HYDROCHLORIDE

Report of Two Cases

MILO D. LEAVITT, M.D.
Fellow in Medicine, Mayo Foundation
AND
CLIFFORD F. GASTINEAU, M.D.
Fellow in Medicine, Mayo Foundation
ROCHESTER, MINN.

INTRODUCTION

Antigenic Nature of Insulin.—Insulin has been proved to be a complete and soluble protein, and like other proteins [1] it may act as an antigen. Precipitins and complement fixation antibodies probably are formed in the susceptible organism after the injection of insulin,[2] but this opinion is not universally accepted. Reagins (circulating antibodies responsible for dermal reactions) frequently can be demonstrated in persons sensitive to insulin by passive transfer.[2]

Chemists have been unable to find any difference in the microscopic appearances, isoelectric points, solubilities and molecular formulas of crystalline insulins from such varying sources as the ox, sheep, hogs and fish.[3] Some workers have maintained that the insulin derived from the pancreases of human beings, cattle, hogs, sheep, bison and dogs has an immunologic identity.[4] Other immunologists have found that beef and pork insulins have antigenic activity in common and also have a "residuum of specificity to the species." [5]

It is difficult to reconcile this evidence of the similarity of animal and human insulin with the allergy which some persons exhibit toward beef

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This work was done under the direction of Dr. C. F. Code and Dr. R. M. Wilder, with the cooperation of Dr. William Locke.

1. Jensen, H.: The Chemical Study of Insulin, Science **75**:614-618 (June 10) 1932.

2. Harten, M., and Walzer, M.: Allergy to Insulin, Liver, Pituitary, Pancreas, Estrogens, Enzymes and Similar Substances, J. Allergy **12**:72-108 (Nov.) 1940.

3. Scott, D. A.: Further Studies on Crystalline Insulin, J. Biol. Chem. **92**: 281-288 (July) 1931.

4. Wasserman, P., and Mirsky, I. A.: Immunological Identity of Insulin From Various Species, Endocrinology **31**:115-118 (July) 1942.

5. Lewis, J. H.: Antigenic Properties of Insulin, J. A. M. A. **108**:1336-1338 (April 17) 1937.

or pork insulin. If the commercial insulin derived from pork or beef is identical with a person's own insulin, then the paradoxic state of hypersensitivity to his own hormones exists. Zondek and Bromberg [6] have given evidence that sensitivity to endogenous steroid hormones may occur, and this hypothesis cannot entirely be discarded in considering allergy to insulin, particularly in cases in which it is associated with diabetes and an insulin refractory state. Other workers [7] have maintained that it is obviously impossible to become sensitive to one's own hormones and have suggested other explanations, such as impurities in the crystalline insulin. This last view has received at least partial confirmation from the work of Hansen and Eyer,[8] who found that recrystallized commercial crystalline zinc insulin gave less severe reactions than did the original crude crystalline form. Another possibility is that the molecular structure of animal insulin is similar enough to that of human insulin to be active in the promotion of carbohydrate metabolism and yet dissimilar enough to act as an antigen.

Insulin modifiers, such as globin and protamine, have been implicated. Page and Bauman [9] found that there were more than seven times as many reactions to the protein, protamine, as to globin. They also found, however, that desensitization to protamine takes place easily. Harten and Walzer [2] considered that positive cutaneous reactions to protamine zinc insulin are always associated with positive reactions to other insulins, such as beef, pork and crystalline insulins. Cohen and Simon [10] implied that protamine zinc insulin causes more reactions than regular insulin.

Types of Hypersensitivity to Insulin.—Allan and Scherer [7] described three classes of reactions: the mild local reaction, the severe local reaction and the generalized reaction. To these may be added the allergy associated with a diminished, and that associated with an exaggerated, response to insulin.

The mild local reaction consists of a stinging sensation at the time of injection, followed by swelling and redness in an area 1 to 4 cm. in diameter, which appear an hour or two later, reach maximal intensity twelve to twenty-four hours later and disappear in one to three days.

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6. Zondek, B., and Bromberg, Y. M.: Endocrine Allergy: I. Allergic Sensitivity to Endogenous Hormones, J. Allergy **16**:1-16 (Jan.) 1945.

7. Allan, F. N., and Scherer, L. R.: Insulin Allergy, Endocrinology **16**:417-430 (July-Aug.) 1932.

8. Hansen, K., and Eyer, H.: Klinische Studien über allergische Krankheiten: V. Insulin-Allergie, Deutsches Arch. f. klin. Med. **174**:133-142 (Oct.) 1932.

9. Page, R. L., and Bauman, L.: Insulins and Insulin Modifiers: Intradermal Studies, J. A. M. A. **124**:704-705 (March 11) 1944.

10. Cohen, A. E., and Simon, F.: Insulin Hypersensitivity, J. Allergy **9**:503-508 (July) 1938.

Tenderness and pruritus may be present. Tuft considered that such mild symptoms do not depend on an antigen-antibody reaction.[11]

The severe local reaction consists of the same redness, swelling, pruritus, tenderness and even local heat, in greater degree. The involved region may reach 5 to 8 cm. in diameter, and then the reaction subsides within a week. Local reactions usually are observed between the third and fourteenth days after injections of insulin are begun. It is uncommon to experience a reaction with the first injection unless insulin has been used previously. Usually if insulin has been used continuously for two weeks without symptoms no difficulty will occur.

The generalized reaction may manifest itself in a variety of ways. A cutaneous reaction is the most common and usually consists of urticaria and angioneurotic edema or rarely of generalized dermatitis. Laryngeal edema may cause some degree of respiratory obstruction, but no death, to our knowledge, has been reported as the immediate result of sensitivity to insulin.[2] Circulatory symptoms of pallor, flushing and palpitation may be followed by some degree of shock. Gastrointestinal symptoms of nausea, vomiting and abdominal cramps may occur. Severe symptoms usually disappear within an hour or two, but discomfort from the urticaria may persist for days. The similarity to serum sickness in symptoms and in time of onset (usually about ten days after treatment is begun) has been noted by others.[2]

Rarely allergy to insulin may be associated with refractoriness to insulin. Lowell[12] found evidence of two distinct antibodies in an instance of refractoriness, one responsible for dermal sensitivity and the other neutralizing the hypoglycemic effects of insulin.

A single instance of exaggerated physiologic response to insulin (hypoglycemia) has been reported as a manifestation of allergy. This manifestation responded to desensitization.[13]

Incidence of Hypersensitivity to Insulin.—Statistics vary greatly, but of the patients receiving insulin, approximately 1 in 10 will experience mild, local reactions, and only 1 in 1,000 will have a systemic reaction.[14] Goldner and Ricketts[15] found only 23 reported instances of generalized sensitivity to crystalline insulin confirmed by allergy studies.

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11. Tuft, L.: Insulin Hypersensitiveness: Immunologic Considerations and Case Reports, Am. J. M. Sc. **176**:707-720 (Nov.) 1928.

12. Lowell, F. C.: Evidence for the Existence of Two Antibodies for Crystalline Insulin, Proc. Soc. Exper. Biol. & Med. **50**:167-172 (May) 1942.

13. Stötter, G.: Desensibilisierungserfolg bei einem hochgradig insulinallergischen Diabetiker, Klin. Wchnschr. **16**:1180-1183 (Aug. 21) 1937.

14. Yasuna, E.: Generalized Allergic Reactions to Insulin: Review of Literature, with Report of Case, J. Allergy **12**:295-306 (March) 1941. Allan and Scherer.[7]

15. Goldner, M. G., and Ricketts, H. T.: Insulin Allergy: Report of Eight Cases with Generalized Symptoms, J. Clin. Endocrinol. **2**:595-602 (Oct.) 1942.

Treatment of Hypersensitivity to Insulin.—Desensitization with insulin has been used effectively in treatment of hypersensitivity to insulin.[16] In this method, increasing amounts of insulin are administered until therapeutic doses are reached. This is required so seldom that no standardized method has been adopted. In a few of the reported cases the initial dose varied from 0.0001 to 1.0 unit, the time required from one to fourteen days and the interval between injections from twenty minutes to twenty-four hours.[17]

In the treatment of mild, local reactions it is usually sufficient to continue the daily injections in spite of symptoms. Such reactions usually diminish or entirely disappear after several weeks.

Changing from one brand of insulin to another and changing from beef to pork insulin or to crystalline insulin are methods of treatment frequently suggested, but conclusive evidence of their effectiveness is rarely presented. Sensitivity to pork insulin but not to beef insulin was verified by skin tests in 1 case by Cohen and Simon.[10]

Histamine desensitization has been used successfully in treatment of hypersensitivity to insulin.[17b] The initial dose of histamine phosphate is 0.002 mg. subcutaneously; injections are made twice daily,[18] and amounts are increased as tolerated. Favorable results from the administration of histaminase were reported by Roth and Horton.[19] Best and McHenry,[20] however, stated that no clinically effective preparation is available. The serum of a rabbit sensitized to the patient's serum was used once successfully.[21]

We have recently published studies of a case in which generalized urticaria was a manifestation of allergy to insulin and the response to diphenhydramine hydrochloride, or "benadryl hydrochloride," was satisfactory.[22] Two similar cases will be described in the present article.

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16. Weitz, M. A.: Insulin Hypersensitivity with Desensitization: Report of a Case, J. Allergy **14**:220-226 (March) 1943.

17. (*a*) Corcoran, A. C.: Note on Rapid Desensitization in Case of Hypersensitiveness to Insulin, Am. J. M. Sc. **196**:359-361 (Sept.) 1938. (*b*) Collens, W. S.; Lerner, G., and Fialka, S. M.: Insulin Allergy: Treatment with Histamin, Am. J. M. Sc. **188**:528-533 (Oct.) 1934. Weitz.[16] Harten and Walzer.[2]

18. Roth, G. M., and Rynearson, E. H.: Use of Histamine and Histaminase in Treatment of Allergic Reaction to Insulin, Proc. Staff Meet., Mayo Clin. **14**: 353-357 (June 7) 1939.

19. Roth, G. M., and Horton, B. T.: Histaminase: Physiologic Effects on Man and Its Therapeutic Value in Medicine, Bull. New York Acad. Med. **16**:570-584 (Sept.) 1940.

20. Best, C. H., and McHenry, E. W.: A Note on Histaminase, J. A. M. A. **115**:235-236 (July 20) 1940.

21. Karr, W. G.; Scull, C. W., and Petty, O. H.: Insulin Resistance and Sensitivity, J. Lab. & Clin. Med. **18**:1203-1211 (Sept.) 1933.

22. Gastineau, C. F., and Leavitt, M. D.: Treatment of Allergy to Insulin with Benadryl: Report of One Case, Proc. Staff Meet., Mayo Clin. **21**:316-319 (Aug. 21) 1946.

Miscellaneous Factors in Local Reactions.—In addition to the insulin itself, other factors may be responsible for the reaction. Animal protein or some other substance from the pancreas not removed in extraction may be present, but commercial insulins are considered to have a nitrogen content "practically the same" [2] as that of crystalline insulin. The alcohol in which the syringe is kept may be responsible for an irritation which appears within a few minutes after injection and subsides within an hour.[7] The preservative in the insulin and the denaturing materials, particularly solution of formaldehyde, and the alcohol used for cleansing the skin may cause reaction.[23]

PROCEDURES USED AND CASES STUDIED

Sensitivity of the skin to insulin and a measure of the effectiveness of treatment with diphenhydramine hydrochloride were determined by measuring the sizes of the flares following intracutaneous injections. Skin-testing procedures were performed in a room maintained at a temperature of 78 F. and at a relative humidity of 40 per cent. Various dilutions of a commercial crystalline zinc insulin U-40 (Lilly) in isotonic solution of sodium chloride were prepared daily for use in testing. A series of testing and control solutions were injected intracutaneously, and colored photographs of the cutaneous reactions were made at intervals of five to ten minutes. The photographs were then projected in actual size, their outlines traced and the areas of the flares accurately determined in square centimeters by means of a planimeter. The maximal size attained by each flare was considered to be the measurement of greatest significance and is recorded in the accompanying tables.

CASE 1.—A white man, 71 years of age at the time of the present study, experienced his first symptoms of allergy at the age of 16 years, when he had several attacks of respiratory difficulty suggestive of asthma. In 1929, without obvious cause, he had an episode of severe urticaria and angioneurotic edema. Since then, at intervals of two to three years, he has had similar, milder attacks, but no etiologic factor has been discovered.

In 1936, at the age of 61 years, the patient noted the gradual onset of polydipsia, polyuria and loss of weight. In 1937 glycosuria and hyperglycemia were discovered, and a diagnosis of diabetes mellitus was established. He was given 10 units of protamine zinc insulin daily, but within a few weeks he found that itching, burning, redness and swelling were appearing at the sites of injection. However, when the insulin was injected into the abdominal wall rather than in the thighs no further difficulty was experienced. (This occurrence is noted frequently in patients with diabetes.) After two months of treatment with insulin, all glycosuria had disappeared and diet alone was sufficient to control the diabetes.

From 1937 to 1946 the diet was restricted moderately and the patient had no glycosuria.

In March 1946, polydipsia, polyuria and glycosuria reappeared. The glycosuria failed to respond to regular insulin in amounts up to 120 units daily, and the patient

23. Cohen and Simon.[10] Harten and Walzer.[2]

complained bitterly of an indefinite feeling of malaise. No local reactions were noted at this time. The malaise ceased when treatment with insulin was discontinued, although the glycosuria was unchanged.

The patient was seen at the Mayo Clinic in July 1946, and treatment with a mixture of protamine zinc insulin and regular insulin was begun. The glycosuria was not affected, but the malaise reappeared. The patient then was placed in the hospital for study. A number of studies designed to demonstrate the possible action of diphenhydramine hydrochloride in diminishing the resistance to the hypoglycemic effects of insulin were inconclusive. During one procedure, 100 units of crystalline insulin was injected intravenously, and within twenty minutes

TABLE 1.—*Direct Skin Tests with Crystalline Insulin in Case 1* *

Solution Injected	Amount, Cc.	Maximal Size of Flare, Sq. Cm.
Isotonic solution of sodium chloride	0.2	0
Insulin U-40	0.2	16.0
Insulin, 1:10	0.2	14.5
Insulin, 1:100	0.2	13.9
Insulin, 1:5,000	0.2	7.2

* A similar series of tests performed in case 2 resulted in generalized urticaria within thirty minutes.

TABLE 2.—*Direct Skin Tests Before and Thirty Minutes After the Oral Administration of One Hundred Milligrams of Diphenhydramine Hydrochloride*

Solution Injected	Amount, Cc.	Maximal Size of Flare, Sq. Cm.		Reduction in Size of Flare, %
		Before Diphenhydramine Hydrochloride	After Diphenhydramine Hydrochloride	
Case 1				
Insulin U-40	0.2	10.3	9.8	4.8
Insulin, 1:10	0.2	17.6	9.8	44.3
Insulin, 1:50	0.2	14.5	6.2	57.2
Isotonic solution of sodium chloride.	0.2	0	0	....
Case 2				
Insulin, 1:5,000	0.2	14.5	2.0	86.2
Isotonic solution of sodium chloride.	0.2	0	0	....

generalized urticaria had developed. On the following day, when the intravenous injection of the same amount of insulin was preceded by the administration of 100 mg. of diphenhydramine hydrochloride orally, no allergic symptoms appeared. Direct skin tests were performed, in which a pronounced sensitivity to crystalline insulin was demonstrated (table 1). The oral administration of diphenhydramine hydrochloride moderately diminished the size of flares resulting from the intracutaneous injection of insulin (table 2). When the drug was mixed with the insulin prior to its intracutaneous injection, the size of the flares was reduced even more (table 3). Prausnitz-Küstner passive transfer tests proved the presence of circulating antibodies (reagins), and diphenhydramine hydrochloride was again found to modify the allergic reaction (table 4).

When the patient was dismissed from the clinic, glycosuria was controlled in a satisfactory manner by the administration of a mixture of 30 units of protamine zinc insulin and 60 units of regular insulin before breakfast and 30 units of regular insulin before the evening meal. In spite of this high requirement of insulin, it was felt that the patient had rather mild diabetes because acetonuria was minimal and the levels of fasting blood sugar did not exceed 200 mg. per hundred cubic centimeters when insulin was omitted.

CASE 2.—A woman 50 years old came to the Mayo Clinic in February 1946 because of recurrent abdominal pain. In 1942 glycosuria had been discovered

TABLE 3.—*Direct Skin Tests with Mixtures of Crystalline Insulin and Diphenhydramine Hydrochloride*

Solutions Injected	Amount, Cc.	Maximal Size of Flare, Sq. Cm.	Reduction in Size of Flare, %
Case 1			
Insulin U-40	0.1	21.2	75.5
Isotonic solution of sodium chloride	0.1		
Insulin U-40	0.1	5.2	
Diphenhydramine hydrochloride 1:1,000	0.1		
Insulin 1:10	0.1	17.0	75.9
Isotonic solution of sodium chloride	0.1		
Insulin 1:10	0.1	4.1	
Diphenhydramine hydrochloride 1:1,000	0.1		
Insulin 1:100	0.1	12.9	100.0
Isotonic solution of sodium chloride	0.1		
Insulin 1:100	0.1	0	
Diphenhydramine hydrochloride 1:1,000	0.2		
Isotonic solution of sodium chloride	0.2	0	
Diphenhydramine hydrochloride 1:1,000	0.2	0	
Case 2 *			
Insulin 1:5,000	0.1	17.0	81.8
Isotonic solution of sodium chloride	0.1		
Insulin 1:5,000	0.1	3.1	
Diphenhydramine hydrochloride 1:1,000	0.1		
Isotonic solution of sodium chloride	0.2	0	
Diphenhydramine hydrochloride 1:1,000	0.2	0	

* Because of the previous severe reaction (generalized urticaria) in case 2 to larger amounts of insulin, only a single injection of insulin in a 1:5,000 dilution was employed in this study.

after a period of loss of weight, polyuria and polydipsia. The patient was given regular insulin and later protamine zinc insulin, but because of increasing local burning, pruritus and redness, use of insulin was discontinued after three months. No difference between the effects of the two insulins was noted. Glycosuria then was controlled by diet until 1943, when she had a miscarriage. She received protamine zinc insulin, with increasingly severe local reactions, for nine days, when a "clear" insulin (probably regular) was substituted. After four days, generalized urticaria and angioneurotic edema appeared, and the patient remained extremely uncomfortable for five days. Glycosuria was controlled by diet until registration at the clinic in February 1946.

The chief complaint was recurrent abdominal pain, and examination revealed that cholecystectomy was necessary immediately. Therefore an estimate of the

degree of sensitivity to insulin was imperative. Four units (0.1 cc.) of a commercial crystalline zinc insulin injected intradermally resulted in a large wheal, with a flare 6 cm. in diameter. Multiple areas of urticaria also were distributed over the body. Four units given subcutaneously caused slight induration, redness and tenderness. On the following day the patient received 150 mg. of diphenhydramine hydrochloride orally one hour before she was given 10 units (0.25 cc.) of crystalline zinc insulin intradermally. This second intradermal injection resulted only in a flare 2 cm. in diameter, and there were no general manifestations.

Cholecystectomy was performed. Postoperative treatment included the administration of 1 liter of a 10 per cent solution of dextrose intravenously on three occasions. To each liter was added 100 mg. of diphenhydramine hydrochloride; 30 units of crystalline insulin was administered subcutaneously at the beginning of

TABLE 4.—*Prausnitz-Küstner Passive Transfer Tests* *

Solutions Injected	Amount, Cc.	Maximal Size of Flare, Sq. Cm.	Reduction in Size of Flare, %
Case 1			
Insulin 1:10	0.1	32.0	58.8
Isotonic solution of sodium chloride	0.1		
Insulin 1:10	0.1	13.4	
Diphenhydramine hydrochloride 1:1,000	0.1		
Insulin 1:50	0.1	20.6	69.9
Isotonic solution of sodium chloride	0.1		
Insulin 1:50	0.1	6.2	
Diphenhydramine hydrochloride 1:1,000	0.1		
Case 2			
Insulin 1:100	0.1	13.9	89.2
Isotonic solution of sodium chloride	0.1		
Insulin 1:100	0.1	1.5	
Diphenhydramine hydrochloride 1:1,000	0.1		
Insulin 1:5,000	0.1	7.2	57.0
Isotonic solution of sodium chloride	0.1		
Insulin 1:5,000	0.1	3.1	
Diphenhydramine hydrochloride 1:1,000	0.1		

* The same solutions injected into the unprepared skin of a normal subject caused no erythema.

each infusion. There was slight induration at each site, but no redness or pruritus. No generalized reaction occurred. Ten days later an elective anterior colporrhaphy was done. Postoperative treatment included the administration of 1 liter of a 5 per cent solution of dextrose intravenously on two occasions. Ten units of crystalline insulin was given subcutaneously with each infusion. Diphenhydramine hydrochloride was not given with either of these injections, and an area of slight redness and induration, 2 to 4 cm. in diameter, resulted. Glycosuria was then controlled by diet alone.

The patient returned in August 1946 for dental extractions. Direct skin tests and Prausnitz-Küstner passive transfer tests were performed at this time. The results are reported in tables 2, 3 and 4. The results of these two procedures were similar to those obtained in case 1, although the degree of sensitivity in case 2 was higher.

RESULTS OF TREATMENT WITH DIPHENHYDRAMINE HYDROCHLORIDE

In these 2 diabetic patients sensitive to insulin, maximal flaring was found to occur from five to thirty minutes after injection; the average time required for this maximal flaring to develop was fifteen minutes after the injection.

Neither the 0.9 per cent (isotonic) solution of sodium chloride nor the 1:1,000 dilution of diphenhydramine hydrochloride in 0.9 per cent solution of sodium chloride caused any flaring in any of the control subjects. The solution of diphenhydramine hydrochloride, however, frequently caused redness, confined to the mechanical wheal, which resulted from the intracutaneous injection of 0.2 cc.

In table 1 is shown the pronounced flaring produced by even high dilutions of insulin in case 1. When similar tests were carried out in case 2, generalized urticaria appeared within thirty minutes as a result of the injection of a total of 9 units of crystalline insulin intracutaneously.

In case 1 the size of the flare produced by undiluted U-40 insulin was diminished only 4.8 per cent, while the flares resulting from 1:10 and 1:50 dilutions were reduced 44.3 and 57.2 per cent respectively by the oral administration of 100 mg. of diphenhydramine hydrochloride. In the patient represented in case 2, who was extremely sensitive and who for this study, therefore, was given only the single injection of insulin in 1:5,000 dilution, the size of the flare was reduced 86.2 per cent (table 2). The dose of 100 mg. used in this procedure is somewhat larger than that ordinarily administered at one time but is within practical limits. The effect of such a dose reaches a maximum within thirty minutes and then gradually diminishes within the next three to six hours.[24]

When diphenhydramine hydrochloride was mixed with the insulin, the allergic reaction was again modified (table 3). With oral administration of the former, flares were reduced in size from about 5 to 86 per cent, while the addition of the drug directly to the solution containing insulin caused reductions of from 75 to 100 per cent.

It seems clinically practical in instances of local allergic reactions to insulin to mix equal quantities (0.5 to 1.0 cc.) of a 1:1,000 solution of diphenhydramine hydrochloride with the daily dose of insulin.[22] This proves to be advantageous in that only 0.5 to 1.0 mg. of diphenhydramine hydrochloride is required to achieve an effect comparable to that obtained by the oral administration of 50 to 100 mg. of the drug. Such a procedure thus eliminates the drowsiness and irritability experienced by some persons receiving the larger doses by mouth. In some persons, however, oral as well as parenteral administration of the drug

24. Leavitt, M. D.: A Study of the Action of Benadryl in the Skin of Human Beings, Thesis, Graduate School, University of Minnesota, 1946.

may be required to control local symptoms. Control of generalized manifestations of insulin allergy most likely will require oral administration of diphenhydramine hydrochloride in addition to that injected with the insulin.

Circulating antibodies (reagins) were demonstrated in the serums of both patients by the Prausnitz-Küstner passive transfer test. This test was performed by injecting 0.2 cc. of the patient's serum intradermally into a nonallergic subject at various sites. Twenty-four hours later, 0.2 cc. of the various dilutions of insulin with and without diphenhydramine hydrochloride were introduced intradermally at the prepared sites. Simultaneous control tests on the unprepared skin of the same subject caused no flaring. When a 1:1,000 solution of diphenhydramine hydrochloride was mixed with the antigen (insulin), the size of flares in the 2 cases was reduced from 57.0 to 89.2 per cent as compared with flares produced by the injection of various dilutions of insulin without the addition of the drug in the prepared sites. Thus it is seen that the reaction between the antigen and the circulating antibodies may be modified by the use of diphenhydramine hydrochloride.

SUMMARY AND COMMENT

Two cases in which allergy to insulin characterized by generalized urticaria was exhibited have been reported.

Studies conducted reveal that in these 2 cases diphenhydramine hydrochloride favorably modified the dermal symptoms of the allergic state and afforded a satisfactory method for treating such symptoms.

In the light of these results, it would seem desirable to have a solution of diphenhydramine hydrochloride available for parenteral administration. Such a solution might be effective in the treatment of localized allergic reactions to a number of injected substances, such as liver extract, hormones, drugs and serums as well as insulin.

Editorial

SUDDEN DEATHS IN THE ARMY

MORITZ and Zamcheck[1] present an interesting survey of the material for autopsy at the Army Institute of Pathology concerning 1,000 sudden deaths from disease of apparently healthy soldiers between 18 and 40 years of age. The most common diseases responsible for rapid, unexpected death among young soldiers were cardiac disease, intracranial hemorrhage and meningococcemia. There were 350 sudden deaths from previously unrecognized cardiac disease, of which about 300 were due to coronary arteriosclerosis. Eight per cent of this group were under 25 years of age, and 22 per cent were younger than 30. White and Negro soldiers were represented in proportion to their numbers in the army. The frequency with which the onset of the fatal attack of coronary insufficiency occurred during a period of strenuous physical exertion lends support to the opinion that violent exercise is dangerous for persons suffering from severe coronary disease. However, this information is not of great practical value to the Army in the prevention of such casualties, because none of the soldiers was suspected of having cardiac disease prior to death and fewer than 25 per cent of them had a history of symptoms suggesting cardiac origin. The authors, therefore, express the opinion that the practicability of conducting complete cardiologic studies on all soldiers who admit having occasional twinges of abdominal or epigastric discomfort is of questionable value. The autopsies in these cases disclosed in all instances severe atherosclerosis of one or both coronary arteries. Thrombotic occlusion was recognized in about 25 per cent, and it was apparent that in most of these the fatal thrombus had begun to form some hours or days before it became symptomatic.

In 69 of 91 reviewed cases of sudden death from nontraumatic intracranial hemorrhage, the bleeding was principally subarachnoid and was either proved or inferred to have resulted from the rupture of a superficial aneurysm of the congenital or berry type. There was some indication that aneurysms of this type are more likely to rupture during a period of violent physical exertion than during sleep. About 20 per cent of these soldiers gave a history of headaches. At autopsy the bleeding was found to be confined to the subarachnoid space in about 65 per cent and was both parenchymatous and subarachnoid in 35 per cent. In 110, or approximately one third of all reported cases of death

1. Moritz, A. R., and Zamcheck, N.: Sudden and Unexpected Deaths of Young Soldiers, Arch. Path. 42:459 (Nov.) 1946.

from meningococcic infections, death occurred within twenty-four hours after the onset of incapacitating symptoms. The incidence was higher in Negroes than in white troops. More than half of the patients in this group died within six hours after coming under medical observation. In approximately 70 per cent of the cases the soldier was reported to have been below par or to have been suffering from a mild infection of the upper respiratory tract prior to the onset of the fulminating phase of the disease. This suggests that a "cold" or minor indisposition complained of by a soldier who may have been exposed to persons with meningococcic infections should not be ignored. The majority of the patients were characterized clinically as suffering from the Waterhouse-Friederichsen syndrome, some with and many without evidence of meningeal invasion. At autopsy, purpura or cutaneous petechiae were recognized in 80 per cent of these men. Focal or massive adrenal hemorrhages were encountered in 71 per cent. In most of the hemorrhagic and nonhemorrhagic adrenal glands, microscopic examination of the cortex disclosed degeneration and necrosis of the tubular type. Adrenal apoplexy occurred in some cases without cutaneous hemorrhages, and again cutaneous purpura was encountered without hemorrhage of the adrenal glands. The impression was gained that adrenal hemorrhage in fulminating meningococcemia was usually preceded by degenerative changes in the cells of the glomerular and fascicular zones of the cortex. Medullary damage was characteristically absent, minimal or terminal.

In addition to the foregoing, there were at least 140 carefully investigated sudden deaths in which the findings at autopsy were essentially normal. They represented more than 10 per cent of all sudden nontraumatic deaths of apparently healthy young men. The racial and age distribution of the soldiers dying of obscure causes corresponded to those of the army as a whole, and weights did not differ from those of soldiers dead of accidental violence or of acute infections. There was no apparent relationship between the onset of the fatal seizure and what the soldier was doing at the time of the attack. Thus, the number of seizures that occurred during sleep or during strenuous exertion was roughly proportional to the number of hours that the average soldier devoted to such activities.

The authors conclude that the methods of examination available to the pathologist are frequently inadequate to disclose either the extent or the nature of certain disorders even though they are of sufficient severity to be incompatible with life.

Correspondence

EOSINOPHILIC GRANLOMA OF BONE SYNONYMOUS WITH SCHÜLLER-CHRISTIAN DISEASE, LIPID GRANULOMA, ESSENTIAL XANTHOMATOSIS OF NORMOCHOLESTEREMIC TYPE AND EOSINOPHILIC XANTHOMATOUS GRANULOMA

To the Editor:—The reader of the article "Eosinophilic Granuloma of Bone: Report of a Case with Multiple Lesions of Bone and Pulmonary Infiltration", by A. Weinstein, H. C. Francis and B. F. Sprofkin, published in this journal (**79**:176 [Feb.] 1947) may become confused on the issue of whether "eosinophilic granuloma of the bone" is a newly discovered disease entity or whether it is a part of a systemic disorder formerly described under different designations such as "Schüller-Christian disease" (Rowland, 1928), "lipid granulomatosis" (by Chester, 1930, and Fraser, 1934) and "essential xanthomatosis of the normocholesteremic type" (Thannhauser and Magendantz, 1937). The following presentation illustrating historically the conception of the pathogenesis of the disease may contribute toward the clarification of some misunderstanding concerning its classification.

Schüller described in 1915 [1] "peculiar defects of the membraneous bones of the skull," referring later, in 1921,[2] to "a peculiar syndrome of dyspituitarism." Christian in 1919 [3] called attention to a clinical syndrome consisting in "defects in membraneous bones, exophthalmos and diabetes insipidus." Hand [4] had already observed a case which belonged in this group, in 1893, but classified the condition as "polyuria and tuberculosis." After the syndrome had been clinically established, the pathologist Rowland in 1929 [5] demonstrated that the histologic lesions characteristic of Schüller-Christian syndrome consist of reticulum cells and histiocytes, cholesterol-containing foam cells and elements of acute inflammation, like esinophils, round cells and polynuclear elements. Rowland considered the development of foam cells as characteristic of the lesion, as had been previously suggested by the dermatologists Weidman and Freeman in 1924 [6] on the basis of two autopsies on patients with lesions of the skin, central nervous system and other organs. In his pioneer work on the histologic changes in Schüller-Christian syndrome Rowland had already described the occasional involvement of the lung and supplemented the description of the pathologic process in the lung with characteristic roentgenograms,

1. Schüller, A.: Ueber eigenartige Schädeldefekte im Jugendalter, Fortschr. a. d. Geb. d. Röntgenstrahlen **23**:12, 1915-1916.

2. Schüller, A.: Ueber ein eigenartiges Syndrom von Dyspituitarismus, Wien. med. Wchnschr. **71**:510, 1921.

3. Christian, H. A.: Defects in Membranous Bones, Exophthalmos and Diabetes Insipidus, in Contributions to Medical and Biological Research, New York, Paul B. Hoeber, 1919, vol. 1, p. 390; M. Clin. North America **3**:849, 1920.

4. Hand, A.: Polyuria and Tuberculosis, Arch. Pediat. **10**:673, 1893.

5. Rowland, R. S.: Xanthomatosis and the Reticulo-Endothelial System, Arch. Int. Med. **42**:611 (Nov.) 1928; Ann. Int. Med. **2**:1277, 1929.

6. Weidman, F. D., and Freeman, W.: Xanthoma Tuberosum: Two Necropsies Dislosing Lesions of Central Nervous System and Other Tissues, Arch. Dermat. & Syph. **9**:149 (Feb.) 1924.

as others did later. Chester in 1930 [7] demonstrated the granulomaous nature of the lesions and classified the disease as "lipid granuloma." The most complete histologic description of solitary lesions of the bone, supported by excellent histologic pictures in color, are found in the paper "Skeletal Lipoid Granulomatosis" by Fraser in 1935. Fraser [8] had already called attention to the endothelial proliferation, the accumulation of eosinophilic cells and the presence of giant cells in the earlier stages of the lesion in "lipoid granuloma." Thannhauser and Magendantz in 1937 [9] demonstrated, on the basis of numerous clinical observations of cases of xanthomatous diseases of heterogeneous origin, that in cases of Schüller-Christian syndrome and those of generalized lipid granulomatosis there was normal cholesterol content of the serum in contrast to that in other groups of xanthomatous disease with hypercholesteremia. For this reason they used the name "essential xanthomatosis of the normocholesteremic type" for Schüller-Christian syndrome and the generalized form of "lipoid granulomatosis." The cholesterol content of the tissues in this disorder in its xanthomatous phase is ten to twenty times higher than that in normal tissue, while the cholesterol level of the serum remains normal. These authors, therefore, contended that the accumulation of cholesterol in the xanthomatous cells in this disorder is not the result of infiltration of cholesterol from the blood stream but is caused by new formation of cholesterol within those cells which gradually develop into xanthoma cells (foam cells). Thannhauser and Magendantz showed in their clinical material and in the cases reported in the literature that various organs (skin ["disseminata" type of xanthoma], osseous system, dura, brain, lung, pleura, liver, spleen and lymph nodes) may be involved singly or in various combinations in the systemic disease under discussion.

Lichtenstein and Jaffe reported in 1940 [10] in a histologic study, cases of solitary lesions of the bone, which they designated as "eosinophilic granuloma of bones." They apparently believed at the time that this type of solitary granuloma of the bone was a disease not hitherto described. They were evidently not familiar with the exhaustive histologic description by Fraser in 1934 of several cases of such disease ("skeletal lipoid granulomatosis") or with case 20 in the article on "Different Clinical Groups of Xanthomatous Diseases" by Thannhauser and Magendantz.

It was not until the studies of Farber and his co-workers [11] and of Holm, Teilum and Christensen [12] that the designation "eosinophilic granuloma" was applied

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7. Chester, W.: Ueber Lipoidgranulomatose, Virchows Arch. f. path. Anat. **279**:561, 1930.

8. Fraser, J.: Lipoid Granulomatosis of the Bones, Brit. J. Surg. **22**:800, 1935.

9. Thannhauser, S. J., and Magendantz, H.: The Different Clinical Groups of Xanthomatous Diseases: A Clinical Physiological Study of Twenty-Two Cases, Ann. Int. Med. **11**:1662, 1938. Thannhauser, S. J.: Lipidoses, New York, Oxford University Press, 1940.

10. Lichtenstein, L., and Jaffe, H. L.: Eosinophilic Granuloma of Bone, with Report of a Case, Am. J. Path. **16**:595, 1940.

11. Green, W. T., and Farber, S.: "Eosinophilic or Solitary Granuloma" of Bone, J. Bone & Joint Surg. **24**:499, 1942. Farber, S.: The Nature of "Solitary Eosinophilic Granuloma" of Bone, Am. J. Path. **17**:625, 1941; The Nature of Some Diseases Ascribed to Disorders of Lipid Metabolism, Am. J. Dis. Child. **68**: 350 (Nov.) 1944.

12. Holm, J. E.; Teilum, G., and Christensen, E.: Eosinophilic Granuloma of Bone: Schüller-Christian's Disease, Acta med. Scandinav. **118**:292, 1944.

not only to solitary lesions of the bone but also to those of "Schüller-Christian syndrome" as well as to the generalized lesions in other organs in the group of diseases formerly classified as "lipid granulomatosis" or clinically designated as "essential xanthomatosis of the normocholesteremic type." Through the histologic studies of Teilum and his co-workers it was demonstrated that the natural history of such an "eosinophilic granuloma" comprised the following phases: (1) a proliferative phase, in which histiocytic proliferation associated with accumulation of eosinophilic leukocytes is observed (see also article by Fraser); in this phase there is no evidence of foam cells; (2) a granulomatous phase, with increase of blood vessels and fibrils, reticular cells and histiocytes, eosinophils and giant cells (Touton cells) and incipient lipid phagocytosis; (3) a xanthomatous phase, with nests and isolated foam cells, and (4) a fibrous stage, considered as a healing phase. These four phases often show no strict demarcation during the course of the disease, and the histologic features of the stages may overlap considerably during the course of the disease. It is evident from the histologic studies of Teilum as well as of Farber that solitary "eosinophilic granuloma" is the monosymptomatic early stage of a systemic disease designated by Chester as well as by Fraser as "lipoid granulomatosis," by Rowland as "Schüller-Christian syndrome" and by Thannhauser and Magendantz, from the clinical point of view, as "essential xanthomatosis of the normocholesteremic type."

The paper of Jaffe and Lichtenstein has caused considerable misunderstanding about the classification of the disease under discussion, as is seen in recent publications cited in the article of Weinstein and his co-workers. The earlier authors as well as Lichtenstein and Jaffe refer to the same disease. The designation of the disease under discussion as "eosinophilic granuloma" is incomplete and therefore misleading, since "eosinophilic granuloma" is not a disease entity but only a phase in the histologic aspect of a distinct clinical syndrome. The formation of xanthoma cells in the later phases of the lesions is as characteristic of the disease as the reticulohistiocytic proliferation and the accumulation of eosinophils in its earlier phases. If one does not prefer to use the older names "Schüller-Christian syndorme," "lipid granulomatosis" or "normocholesteremic xanthomatosis," one should think of a classification which at least refers to the two outstanding histologic phases of the granuloma, namely, the proliferative and eosinophilic phase and the xanthomatous phase. The designation of the localized and systemic disorder as "eosinophilic xanthomatous granuloma" seems to be more appropriate, even if it does not embrace the reticulohistiocytic proliferation of the early lesion. Such a name would also prevent further misunderstanding in the conception and classification of this disorder.

Joseph H. Pratt Diagnostic Hospital.

S. J. THANNHAUSER, M.D., PH.D., Boston.

PENICILLIN IN TREATMENT OF KERATOSIS BLENNORRHAGICA

To the Editor:—My attention was recently called to an article which appeared in the ARCHIVES by Freireich, Schwartz and Steinbrocker—"Penicillin in the Treatment of Keratosis Blennorrhagica with Polyarthritis" (**79**:239-250 [Feb.] 1947).

In this paper the authors state that "no record of therapy for keratosis blennorrhagica with penicillin has appeared in the literature." May I respectfully call

your attention to my article, "Keratoderma Blennorrhagicum: Brief Review and Report of a Case Treated with Penicillin," which appeared in the *American Journal of Syphilis, Gonorrhea and Venereal Diseases* (**29**:361-371 [May] 1945)?

E. M. SATULSKY, M.D., Elizabeth, N. J.

To the Editor:—There is no doubt that Dr. Satulsky can claim priority in the use of penicillin in keratosis blennorrhagica. However, in all fairness, one should quote the entire sentence from our article, which reads, "To our knowledge, no record of this type of therapy for keratosis blennorrhagica has appeared so far in the literature." Unfortunately, Dr. Satulsky's article escaped our attention when our work was submitted. When the first draft of our paper was prepared, his article had not yet been published. The patient in our case 1 was started on medication with penicillin on Oct. 14, 1944, and the patient in case 2 received it on Oct. 2, 1944, approximately seven months before the appearance of his article in the literature. Although there is no question that his patient, who received his first dose of penicillin on Jan. 24, 1944, obtained this type of therapy before our patients did, it was without any knowledge of his work that we instituted similar treatment.

A. W. FREIREICH, M.D., Malverne, N. Y.

News and Comment

GENERAL NEWS

Conference on Antihistamine Agents in Allergy.—A conference on antihistamine agents in allergy will be held on Oct. 3 and 4, 1947, under the auspices of the New York Academy of Sciences. The program follows:

FRIDAY MORNING, OCTOBER 3, 9:30 A. M.—12:30 P. M.
Chairman: DR. FREDRICK F. YONKMAN

"The Pharmacodynamics of Histamine," Sir Henry H. Dale, formerly Director of the National Institute for Medical Research, Mount Vernon House, N. W. 3, England

"The Role of Histamine and Other Metabolites in Anaphylaxis," Dr. Carl A. Dragstedt, Professor of Pharmacology, Northwestern University Medical School, Chicago

"The Role of Blood Platelets and Leukocytes in Anaphylaxis," Dr. M. Rocha e Silva, Professor of Pharmacology and Biochemistry, Instituto Biologica, Sao Paulo, Brazil

FRIDAY AFTERNOON, OCTOBER 3, 2:00 P. M.—5:00 P. M.
Chairman: DR. ROBERT COOKE

"The Immunologic Aspects of Anaphylaxis and Allergy," Dr. M. W. Chase, Rockefeller Institute, New York

"The Detoxification of Histamine," Dr. E. T. Waters, Banting and Best Department of Medical Research and Department of Physiology, University of Toronto, Toronto, Canada

"Histamine-Azo-Proteins in Anaphylaxis and Allergy," Dr. N. Fell, Camp Detrick, Frederick, Md.

SATURDAY MORNING, OCTOBER 4, 9:30 A. M.—12:30 P. M.
Chairman: DR. GEORGE RIEVESCHL JR.

"Introduction to Antihistamine Agents and Antergan Derivatives," Dr. D. Bovet, Professor of Pharmacology, University of Rome, Italy

"The Activity of Pyribenzamine and Related Compounds with Special Reference to Their Mode of Action," Dr. Rudolf L. Mayer, Division of Research, Ciba Pharmaceutical Products, Inc., Summit, N. J.

"The Pharmacology of Benadryl and the Specificity of Antihistamine Drugs," Dr. Earl R. Loew, Department of Pharmacology, University of Illinois College of Medicine, Chicago

SATURDAY AFTERNOON, OCTOBER 4, 2:00 P. M.—5:00 P. M.
Chairman: DR. SANFORD B. HOOKER

"Antistine and Related Imidazolines," Dr. Rolf Meier, Medical Director, Ciba Limited, Basel, Switzerland, and Professor of Pharmacology and Therapeutics, University of Basel, Switzerland

"The Mechanism of Action of Antihistamine Agents with Special Reference to Their Mode of Action in the Skin," Dr. Charles F. Code, The Mayo Foundation, Rochester, Minn.

"Antihistamine Therapy, Experimental and Clinical Correlation," Dr. Samuel M. Feinberg, Department of Allergy, Northwestern University Medical School, Chicago

Requests for further information and inquiries about attending the conference should be addressed to the executive secretary of the Academy, Eunice Thomas Miner, Central Park West at Seventy-Ninth Street, New York 24.

Poliomyelitis Conference Set for Georgia Warm Springs September 15, 16 and 17.—Marking the twentieth anniversary of the founding of Georgia Warm Springs, a three day clinical conference on diagnosis and treatment of poliomyelitis will be held at Warm Springs, Ga., on September 15, 16 and 17.

The clinical conference will be led by approximately twenty of the nation's authorities in the fields of neurology, pathology, pediatrics, orthopedics, physical medicine and internal medicine, who will present papers reviewing the advances in the knowledge of poliomyelitis in these fields.

The papers and discussions will constitute the material for a new book on diagnosis and treatment of the disease for publication in 1948. Clinical demonstrations of modern methods of treatment will be given by the medical staff of the Warm Springs Foundation.

Physicians interested in attending this conference should send inquiries to the Georgia Warm Springs Foundation, 120 Broadway, New York 5, N. Y. A complete program of the meeting will be available on request.

Sixth International Short Wave Congress.—The Sixth International Short Wave Congress will be held in Amsterdam, Netherlands, July 19 to 24, 1948. Those who wish to take part in the congress are requested to communicate with Dr. J. Samuels, Weteringschans 73, Amsterdam, Netherlands. Manuscripts should be sent before April 15 at the latest to W. F. K. Gouwe, Lutten-Dedemsvaart, Netherlands.

Graduate Fortnight, New York Academy of Medicine.—A graduate fortnight will be held again this year at The New York Academy of Medicine, October 6 to 17, inclusive. It will be devoted to the study of disorders of metabolism and the endocrine glands.

Book Reviews

Clinical Electrocardiography. By David Scherf, M.D., and Linn J. Boyd, M.D. Second edition. Price, $8. Pp. 267, with 243 illustrations. Philadelphia: J. B. Lippincott Company, 1946.

The second edition of this excellent treatise on electrocardiography has been revised and reset in a two column format. This change only partly overcomes a common and trying minor annoyance to one studying books of this kind carefully, namely, that the discussion of a tracing often follows a page or two behind its occurrence in the book.

As the authors mention in their preface, more and more physicians, with the ready availability of recording devices, are dabbling in electrocardiography, and unwarranted ideas about the simplicity of interpretation are widespread, the limitations and uncertainties of the method being inadequately stressed. This misconception is carefully emphasized, and another fault of many textbooks, i. e., the tacit assumption that certain basic useful working hypotheses have been established as fact, is avoided. Adherence to these principles produces a book which neophytes will find confusing and difficult but which will reward them richly for careful study and which is invaluable to the mature student.

The generally superb quality of the discussions is seriously marred by the fact that chest leads are considered separately in a single chapter and then the discussion is largely confined to CR_3 and CR_4. Indeed, in the whole chapter on myocardial infarction only one chest lead is reproduced, and none is shown in the chapter on the exercise tolerance test in coronary sclerosis. The freedom with which the authors use as equivalents the terms "myocardial infarction" and "coronary thrombosis" is regrettable.

The chapters on pericarditis, pulmonary embolism and changes associated with endocrinopathies are required reading for all who interpret electrocardiograms, and the lengthy sections on the arrhythmias are the best available source of thoughtful and objective information on this subject. Interference dissociation, reciprocal rhythm, parasystole and the concept of exit blockade are discussed in detail.

Despite the minor criticisms mentioned, this book adequately presents a summary of the practical aspects of electrocardiography and provides excellent correlation of electrocardiographic with clinical findings.

Principles of Dynamic Psychiatry. Including an Integrative Approach to Abnormal and Clinical Psychology, with a Glossary of Psychiatric Terms. By Jules H. Masserman. Price, $4. Pp. 322, with 4 illustrations. Philadelphia: W. B. Saunders Company, 1946.

There is a growing tendency for psychiatry and internal medicine to grow closer. Older clinicians say that this is not a new idea; younger ones, however, are inclined to talk of psychosomatic medicine and seem to feel that instead of caring for ill patients with the help of insight and sympathy, as Francis Peabody suggested, they can accomplish better results by more elaborate psychiatric methods. A book such as this is extremely helpful. It presents in clear and readable form the ideas of a psychiatrist who has worked in the field of internal medicine; it describes the manner in which the complex problems of thought are being approached by experts, and it outlines current knowledge of the methods of measuring behavior. The book also has two other valuable features. The first is its glossary; here, as the author says, the internist can find the meaning of about twelve hundred of the more obscure terms found in current psychiatric literature, thus learning to translate into his own vernacular articles or books which, though printed in English, often seem unduly hard to comprehend. The second is an admirable bibliography and index.

On the whole, the work deserves high praise. Medical students and teachers are certain to find it a useful tool, while ordinary readers can learn a great deal from it.

Electrocardiography. By Louis N. Katz, M.D. Second edition. Price, $12. Pp. 883, with 525 illustrations. Philadelphia: Lea & Febiger, 1946.

The ARCHIVES (**69**:368 [Feb.] 1942) reviewed the first edition of this book in a complimentary manner. It seemed a scholarly work and was handsomely printed and profusely illustrated. The only possible complaint—and this was minor—concerned the author's meticulousness; parts of the book made rather heavy reading because of his zealous attention to detail.

The second edition is a revision of the first; it is 203 pages longer, containing more than a hundred additional illustrations and selling at an increased cost of $2. It continues to be an admirable text, so that all the pleasant things said of the first edition can be repeated. It is certain to achieve great popularity.

A Bibliography of Infantile Paralysis, 1789-1944, with Selected Abstracts and Annotations. Prepared under Direction of the National Foundation for Infantile Paralysis, Inc. Edited by Morris Fishbein, M. D., Editor, Journal of the American Medical Association. Compiled by Ludvig Hektoen, M.D., Chief Editor, Archives of Pathology, and Ella M. Salmonsen, Medical Reference Librarian, John Crerar Library, Chicago. Cloth. Price, $15. Pp. 672. Philadelphia: J. B. Lippincott Company, 1946.

This is without question the finest bibliography on any subject ever published. Probably no bibliography has ever been as completely and carefully compiled. Every reference has been checked and rechecked with the original article. The periodical literature of the world has been examined and the references to all important clinical and investigative work on infantile paralysis recorded. The volume starts with the first definite descriptions of the disease by Underwood in 1789 and ends with references to articles published in December 1944.

The book is beautifully printed on excellent paper in large clear type. If the term artistic can be applied to a bibliography, this work certainly merits such a designation. The page is of convenient size and arrangement for easy reading, and the volume, in spite of the 672 pages, is light and readily handled.

Over 8,750 references to infantile paralysis are included. These are largely from periodical literature, as is proper. The material in textbooks, systems of medicine and encyclopedias is rarely new and is generally a compilation from more detailed articles in the current literature; hence little or no attention was devoted to such sources and to the more general discussions of poliomyelitis found in publications of boards of health and in those on general health education.

This bibliography has a unique arrangement, the references being first listed under the year of publication. It is interesting to note the gradual increase in the number of titles from 1789, when the first references appeared, to the beginning of the twentieth century. From then on the greatly augmented publication of medical journals and the increasing interest in poliomyelitis sharply accentuate the number of pertinent articles. The arrangement of references by years allows a reader to ascertain readily what progress has been made at any period and to determine whether certain articles would be of purely historical value and what papers, especially those dealing with research, may be considered of immediate importance.

Under the respective yearly headings, the titles are arranged alphabetically according to authors, each being numbered for facility in location in both the author and subject index. The number and author's name are printed in bold type, making quick reference possible. The complete title in the original language follows, with translation into English when other than English was used. The name of the publication and the volume, page and date are given in the form approved by *The Journal of the American Medical Association.*

An especially valuable and time-saving addition to the usual bibliography is the concise abstract appended to the majority of the references. These are well written and give the essential facts of the article, so that any worker can quickly determine whether the entire paper should be read. Also many of these abstracts are from journals not readily available or from articles in foreign languages not understood by many. The wealth of detailed material in these abstracts is surprising, and one gains the impression that the pith of the paper is presented.

The breadth of this stupendous work can be partially understood by the range of the languages translated. In addition to the American and English publications, which are particularly rich in clinical and virus research work on infantile paralysis, the following languages are covered: Danish, French, German, Hungarian and other Slavic languages, Icelandic, Italian, Japanese, Norwegian, Portuguese, Spanish, Swedish and Russian.

The complete author and subject indexes will prove invaluable to everyone working on infantile paralysis. Thanks to the system of numbering all references, all the articles published between 1789 and 1945 by any individual author or on any particular phase of the subject can be instantly determined. The subject index is exceedingly complete, with alphabetically arranged subheadings following the list of numbers of all references covering the particular subject. For example, under the heading "contagiousness" there are thirty-eight subheadings, each with the numbers of the references covering this particular phase of the subject. The main headings are in bold type, and all annotations are in type sufficiently large to make for easy reading.

Such a monumental work would not have been undertaken and could not have been brought to a successful conclusion without the financial support of a great foundation. It seems fitting that this outstanding publication was made possible by the National Foundation for Infantile Paralysis. Great credit is due the administration of this foundation, particularly its president, Basil O'Connor, for conceiving the need for such a work and wholeheartedly backing its production. The reviewer also wishes to commend particularly the editor, Morris Fishbein, whose guiding interest and enthusiastic cooperation insured its successful and early completion. The vital roles played by Ludvig Hektoen and Ella Salmonsen can best be judged by perusing the work.

It is proposed to issue a supplementary volume every two years and at the end of ten years to compile these into a second single volume bibliography.

This bibliography of infantile paralysis with selected abstracts and annotations can well serve as the model for all future bibliographies on any medical subject. It should be in the library of everyone concerned in clinical or laboratory investigations of poliomyelitis.

Howell's Textbook of Physiology. Edited by John F. Fulton, M.D., with the collaboration of Donald H. Baron and others. Fifteenth edition. Price, $8. Pp. 1,304, with 507 illustrations. Philadelphia: W. B. Saunders Company, 1946.

In preparing the fifteenth edition of this classic American text, the editor has enlisted the collaboration of a group of associate editors, each responsible for one of the ten sections of the book. Each of them has secured various contributors for different portions of the text. In a field such as physiology, in which additional factual knowledge is being accumulated so rapidly and in which viewpoints, of necessity, must change, it is a difficult or impossible task for one person to present a picture in clear perspective. In his organization of the task before him, Dr. Fulton has succeeded in carrying out Dr. Howell's guiding principle as stated in the previous edition—"First, the importance of simplicity and lucidity in the presentation of facts and theories, and, second, the need of a judicious limitation of the material selected." Both objectives have been attained in the preparation of a ready reference text for students and practitioners. In spite of a large amount of rewriting necessary because of the date and new points of view, Dr. Fulton has succeeded in carrying out Dr. Howell's objective and in continuing the book as the leading American text, indispensable to every physician's library.

Exercises in Electrocardiographic Interpretation. By Louis N. Katz, M.D. Second edition. Price, $6. Pp. 288, with 141 illustrations. Philadelphia: Lea & Febiger, 1946.

The ARCHIVES (**69**:160 [Jan.] 1942) reviewed the first edition of this book, characterizing it as an outcropping of a tendency toward reviving, in a new field, Dr. Richard C. Cabot's plan of "case teaching in medicine" by the study of paper patients. The volume described how to interpret electrocardiograms and then presented a series of case reports, each accompanied with beautifully reproduced electrocardiographic tracings pertinent to the cases described and intelligently and skilfully interpreted. The prediction was made that such a method of teaching electrocardiographic interpretation might prove helpful to many groups of physicians and students.

This prophesy has been fulfilled. As the author says, the reception of the first edition demonstrated that it helped to fill a significant need. He now has revised it, making certain changes in the cases reported and editing his work thoroughly. Thus the second edition follows the general plan of the first, is more up-to-date and is an improved model. He hopes that it will be as useful as its predecessor. It promises to be even more popular.

Roentgen Diagnosis of Diseases of the Gastrointestinal Tract. By John T. Farrell Jr., M.D. Price, $5.50. Pp. 271, with 193 illustrations. Springfield, Ill.: Charles C Thomas, Publisher, 1946.

This is an interesting text, dealing with its subject in an orderly and precise manner. One of its most original features is its typography. While disorders of the gastrointestinal tract are listed with due orthodoxy, those which are usually detected by roentgenologists, those which are discussed in this text and those which are illustrated are listed in bold-faced type; those which are discussed but not illustrated are listed in light-faced type, and those which can be detected roentgenologically but which are neither discussed nor illustrated are listed in italics. The nomenclature used is that outlined in "Standard Nomenclature of Disease" and approved by the American Medical Association.

Once a reader familiarizes himself with these features, he finds the book readable and easy to follow. There are many illustrations which reproduce roentgenograms with unusual clarity. The descriptive writing is well done, clearly by a teacher who knows how to express his ideas forcibly and succinctly. Without doubt this is a useful volume, promising to be popular with radiologists, clinicians and students.

Allergy. By Erich Urbach, M.D., and Philip M. Gottlieb, M.D. Second edition. Price, $12. Pp. 968, with 410 illustrations. New York: Grune & Stratton, Inc., 1946.

The ARCHIVES reviewed the first edition of this book (**72**:427 [Sept.] 1943). There were a few minor criticisms, chiefly the authors' coinage of words. They manufactured tongue twisters like "allergic pathergy," "parallurgy" and "allergization" instead of using more understandable expressions. Also they devoted considerable space to "propepton" therapy, which not all American allergists had accepted. On the whole, however, the review was complimentary, praising the book's thoroughness and the manner in which its subject matter was arranged and mentioning almost with awe its mammoth size.

Clearly, it has had a successful career, for now the second edition is at hand. This continues to be a large and handsome affair, discussing in detail almost every phase of its title. The authors still use new words which are a trifle difficult for an older internist to comprehend. "Propepton" continues to receive considerable attention. A double column format has been adopted to prevent overbulkiness.

The bibliography has been brought up-to-date and appears to be complete. The second edition promises to achieve the same degree of popularity as did its predecessor. Certainly it is a commendable text.

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